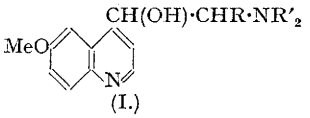
22. *Studies in the Series of 4-Substituted Quinolines.*

By J. W. Cornforth and (Mrs.) R. H. Cornforth.

Some attempts to prepare analogues of quinine are described.

The work described here was directed to the synthesis of quinine analogues of type (I; R = Me). King and Work (*J.*, 1940, 1311) have described a series of compounds in which R = H; some of these were active antimalarials. The method adopted was to condense the bromo-ketone (II; R = H) with secondary bases and to reduce the resulting keto-amines (III; R = H) catalytically. The yield in certain cases was reduced by fission of secondary amine during the reduction, with formation of the carbinol (IV; R = H).

This route was first investigated. The condensation of ethyl quininate and ethyl propionate (Rabe and Pasternack, *Ber.*, 1913, **46**, 1033) was improved and hydrolysis gave 6-methoxy-4-



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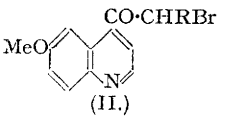

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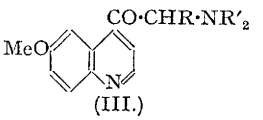

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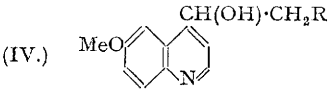
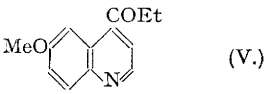
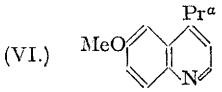
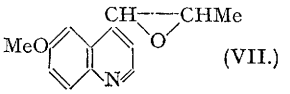






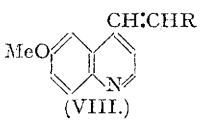


propionylquinoline (V). An alternative route to (V) was also examined, 6-*methoxy*-4-*propylquinoline* (VI) being prepared from *p*-anisidine and 2-chloroethyl propyl ketone (cf. Blaise and Maire, *Bull. Soc. chim.*, 1908, **3**, 658; Kenner and Statham, *Ber.*, 1936, **69**, 16). Oxidation of (VI) with selenium dioxide, or condensation with benzaldehyde or chloral, gave no result.

Bromination of the ketone (V) gave the *hydrobromide* of (II; R = Me), and this was condensed with various secondary amines. The yield was diminished by side reactions, and the products (III; R = Me) were best isolated as their dipicrolonates. The ketone-bases (III; R = Me) were reduced under a variety of conditions. Only in the case of the piperidyl compound could the desired product be obtained, namely 6-*methoxy*-4-(1-*hydroxy*-2-N-*piperidylpropyl*)*quinoline* (I; R = Me, NR'_2 = *N*-piperidyl). In the other cases tried, *e.g.*, di-*n*-butylamine, complete fission occurred, with production of either the ketone (V) or 6-*methoxy*-4-*quinolylethylcarbinol* (IV; R = Me), according to conditions; on one occasion the propylquinoline (VI) was isolated. The problems presented by this stage were still unsolved when the work had to be abandoned.

iso*Nitroso*-6-*methoxy*-4-*quinolyl ethyl ketone* was also prepared; reduction with stannous chloride gave the carbinol (IV; R = Me) with fission of ammonia.

If 6-methoxy-4-(1 : 2-epoxypropyl)quinoline (VII) could be prepared, it might prove a useful source of substances of type (I; R = Me). Attempts were made to prepare this oxide from 4-propenyl-6-methoxyquinoline (VIII; R = Me), which was isolated as the *picrate* from the condensation of 6-methoxylepidine with acetaldehyde in the presence of a little acetic acid. However, no useful product could be obtained from the oxidation of (VIII, R = Me) with perbenzoic acid. The oxidation of 6-methoxylepidine and of 6-methoxy-4-styrylquinoline with perbenzoic acid was examined; 6-*methoxylepidine* N-*oxide* and 6-*methoxy*-4-*styrylquinoline* N-*oxide* were obtained. In the case of the styryl-quinoline more than one molecular proportion of perbenzoic acid was consumed, but the *CN*-dioxide was either not formed or else too unstable to be isolated. It was found that these *N*-oxides are more resistant to reduction than the oxides of aliphatic tertiary amines; *e.g.*, reduction was not effected by sulphur dioxide. This observation makes it probable that the "quinine *CN*-dioxide" of C. H. Boehringer Söhne (D.R.-P. 497,098; *Chem. Zentr.*, 1930, II, 584) is in effect the *NN*-dioxide, and the "*C*-monoxide" the *N*-oxide of the quinoline nitrogen, for it was apparently concluded that the second oxygen atom could not be attached to nitrogen because of its stability to sulphur dioxide. The properties of the monoxide (sensitivity to light, tendency to solvation) also suggest an *N*-oxide.



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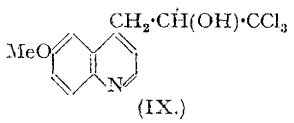

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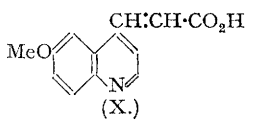

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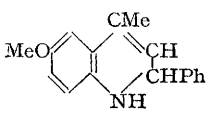

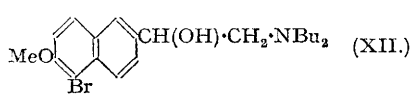

(XII.)

The preparation of 6-methoxy-4-vinylquinoline (VIII; R = H) was also undertaken. Condensation of 6-methoxylepidine with chloral gave 6-*methoxy*-4-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoline* (IX). This was not affected by stannous chloride in acetone; reduction with

zinc in alcohol–acetic acid gave a little 6-methoxy-4-propylquinoline (VI). Hydrolysis of (IX) with alcoholic potash gave β-6-*methoxyquinolyl*-4-*acrylic acid* (X).

Addition of hydrogen bromide to (X) followed by treatment with hot concentrated potassium carbonate solution gave a small amount of 6-methoxy-4-vinylquinoline, isolated as the *picrate*. The condensation of α-picoline with acetaldehyde by means of phenyl-lithium (Walter *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 2771) has been reported. This was tried with 6-methoxylepidine as an alternative approach to the propenyl compound (VIII; R = Me). However, addition of phenyl-lithium took place instead of hydrogen exchange, and the product was 6-methoxy-2-phenyl-4-methylquinoline, apparently produced by disproportionation of the dihydroquinoline (XI).

A compound of the naphthalene series, 1-bromo-2-methoxy-6-(2-dibutylamino-1-hydroxyethyl)naphthalene (XII), was prepared, as the *dipicrate*, by condensation of the corresponding bromoacetylnaphthalene with dibutylamine, followed by reduction.

In the course of preparation of various secondary amines, di-*n*-amylamine was prepared (cf. King and Work, *loc. cit.*) by reduction of *benzyldi*-n-*amylamine*, which was formed along with *benzyl*-n-*amylamine* by alkylation of benzylamine with amyl bromide.

Experimental.

6-*Methoxy*-4-*propionylquinoline* (V).—Ethyl quininate (82 g.) with ethyl propionate (40 g.) and benzene (120 c.c.) were treated with sodamide (20 g.). It was unnecessary to powder the sodamide provided that the lumps were not too large. The mixture was heated under reflux for 70 hours, then worked up as described by King and Work (*loc. cit.*). The crude keto-ester was hydrolysed by heating with sulphuric acid (250 c.c. of 25%) for two hours on the steam-bath. The basic ketone, recovered by means of ether in the usual manner, was extracted with hot light petroleum (b. p. 40—60°). On evaporation of the decanted solution the ketone (36 g.) crystallised and was then sufficiently pure. In addition to ethyl quininate and quininamide, quininic acid was also recovered from the reaction mixture. The quininamide was hydrolysed and the total quininic acid esterified and united with the ethyl quininate, giving a total recovery of 30 g. The yield of ketone was thus 75%, based on unrecovered ethyl quininate.

6-*Methoxy*-4-*propylquinoline* (VI).—*p*-Anisidine (9·1 g.), hydrated stannic chloride (13 g.), and alcohol (10 c.c.) were mixed and heated on the steam-bath during the addition of propyl 2-chloroethyl ketone (5 g.) dropwise during 1½ hours. After 8 hours' refluxing the mixture was made alkaline and the ether-soluble product distilled. *p*-Anisidine (4·2 g.) was recovered. The fraction, b. p. 145—200°/10 mm. (5·2 g.), was warmed with acetic anhydride (5 c.c.) for 15 minutes. Dilute acid and ether were added. The aqueous acid solution was treated with excess of ammonia, and the base taken up in ether and again extracted with dilute acid. This second extraction was necessary to remove a small amount of *p*-acetanisidide, which is appreciably extracted by acids. The *base*, recovered in the usual way, was distilled, b. p. 194—200°/10 mm. (2·9 g.), and solidified on cooling. Crystallisation from light petroleum gave colourless prisms, m. p. 56—57° (Found: C, 77·7; H, 7·4. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5%).

In one experiment when the base was liberated with sodium carbonate, crystals separated and were collected and recrystallised twice from methanol to give colourless prisms, m. p. 97°, apparently of a *carbonate* [Found: C, 68·4; H, 7·1; N, 6·0. $(C_{12}H_{15}ON)_2,H_2CO_3$ requires C, 69·0; H, 7·1; N, 6·2%]. The *picrate* crystallised from acetone in yellow prismatic needles, m. p. 196—197° (Found: N, 13·0. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires N, 13·0%).

6-*Methoxy*-4-(α-*bromopropionyl*)*quinoline Hydrobromide*.—The ketone was dissolved in hydrobromic acid (24%) and brominated by addition of the calculated quantity of bromine, either carried by a stream of air or dissolved in hydrobromic acid. The crystalline *hydrobromide* separated slowly; 39 g. were obtained from 24 g. of ketone. Crystallisation from acetone gave pale yellow prisms, m. p. 192—193° (decomp.). Analysis indicated some loss of hydrogen bromide on drying (Found: C, 42·5; H, 3·5; N, 4·0; Br, 38·0. $C_{13}H_{12}O_2NBr,HBr$ requires C, 41·6; H, 3·5; N, 3·7; Br, 42·3%).

6-*Methoxy*-4-(α-N-*piperidylpropionyl*)*quinoline Dipicrolonate*.—The hydrobromide of (II; R = Me) (1·9 g.) was added to piperidine (1·25 g.) in dry ether (5 c.c.). After one hour the piperidine hydrobromide (1·4 g.) was collected. The filtrate was washed well with water, and the ether removed at low pressure. The residue was dissolved in dry acetone (100 c.c.) containing picrolonic acid (2·8 g.). An orange-red crystalline solid separated rapidly (2·7 g.). Recrystallised from much acetone, it formed needles, which decomposed about 160—170° according to the rate of heating (Found: C, 55·4; H, 4·7; N, 16·0. $C_{18}H_{22}O_2N_2,2C_{10}H_8O_5N_4$ requires C, 55·2; H, 4·6; N, 17·0. $C_{18}H_{22}O_2N_2,2C_{10}H_8O_5N_4,C_3H_6O$ requires C, 55·65; H, 5·0; N, 15·8%).

6-*Methoxy*-4-(1-*hydroxy*-2-N-*piperidylpropyl*)*quinoline*.—The above dipicrolonate (2·7 g.) was ground with hydrochloric acid (10 c.c. of 5N), and the picrolonic acid collected and washed with more acid (15 c.c. of 5N). The base was recovered from the filtrate by means of alkali and ether, all heating being avoided; it was dissolved in hydrochloric acid (50 c.c. of N) and hydrogenated at room temperature and pressure in the presence of platinum oxide (25 mg.). The reduction was interrupted when 1 mol. of hydrogen had been taken up. The basic product was recovered as usual and treated with picrolonic acid (1·6 g.) in acetone (50 c.c.). A yellow, sparingly soluble picrolonate soon separated (1·8 g.). It was decomposed with 5N-hydrochloric acid as above. Isolated in the usual way, the *base* soon crystallised. Recrystallisation from ether gave stout colourless prisms, m. p. 118—119° (Found: C, 72·2; H, 7·8; N, 9·2. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·0; N, 9·3%). The dihydrochloride formed colourless needles from acetone–alcohol, m. p. 137—138° (decomp.). On a larger scale, isolation of the product

through the picrolonate was omitted. From 7·8 g. of hydrobromide were obtained 1·35 g. of carbinol base.

Experiments with Dibutylamine.—The bromo-ketone hydrobromide (5 g.) was added to dibutylamine (5·5 g.; freshly distilled, b. p. 159—160°) in dry acetone (10 c.c.). After one hour at room temperature and 45 minutes at 45°, the solution was diluted with dry ether, the dibutylamine hydrobromide (5 g.) collected, the filtrate evaporated at low pressure, and the residue washed well with water. Addition of picrolonic acid (7·4 g.) in acetone now gave the orange dipicrolonate (6·8 g.) of the keto-base. This could not be recrystallised owing to its insolubility and sensitivity to heat. The free keto-base was prepared from the picrolonate in the manner already described; the base was used in the following reductions.

(1) Catalytic reduction in acid solution gave the ketone (V), isolated as the *picrate*, yellow needles, m. p. 174—175°, from acetone (Found: C, 51·7; H, 3·8. $C_{13}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 51·4; H, 3·6%). Reduction over platinum in the presence of ferrous sulphate gave, in acid or neutral solution, 6-*methoxy*-4-*quinolylethylcarbinol* (IV; R = Me), which crystallised in small compact prisms, m. p. 102°, from a little benzene (Found: C, 72·0; H, 7·1. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9%); *hydrochloride*, colourless prisms from methanol, m. p. 224° (decomp.) (Found: N, 5·7. $C_{13}H_{15}O_2N,HCl$ requires N, 5·5%); *picrate*, deep yellow prismatic needles from acetone, m. p. 178° (Found: N, 12·6. $C_{13}H_{15}O_2N,C_6H_3O_7N_3$ requires N, 12·6%). Fractionation by the method of differing basicities was generally used to examine the products.

(2) Reduction with zinc dust in cold acetic acid gave the carbinol (IV; R = Me), isolated through the picrolonate.

(3) Reduction with aluminium amalgam in faintly acid solution gave (through the picrolonate), 6-methoxy-4-propylquinoline, m. p. and mixed m. p. 57—58°.

(4) Reduction with sodium amalgam in weakly acid solution gave the ketone (V), isolated in good yield as the picrate.

(5) Reduction with aluminium *iso*propoxide in *iso*propanol gave an intractable product.

iso*Nitroso*-6-*methoxy*-4-*quinolyl Ethyl Ketone.*—Sodium (0·35 g.) was dissolved in alcohol (8 c.c.). Methoxy-4-propionylquinoline (3·15 g.), mixed with freshly distilled *iso*amyl nitrite (1·8 g.), was added gradually. After two days at 0° water and ether were added. The aqueous solution was treated with acetic acid (4·5 c.c. of 20%). The gelatinous solid was collected and dissolved in hot alcohol (300 c.c.). On cooling, felted needles (2 g.) were deposited. After another crystallisation the iso*nitroso*-derivative had m. p. 228° (Found: after drying at 100°: C, 63·7; H, 4·8. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9%). Reduction with stannous chloride in hydrochloric acid gave the carbinol (IV; R = Me), isolated as the hydrochloride.

6-*Methoxy*-4-*propenylquinoline* (VIII; R = Me).—6-Methoxylepidine (11·5 g.) with acetaldehyde (12 c.c.; pure), quinol (50 mg.), and acetic acid (5 drops) were heated in a sealed tube at 200° for 14 hours. The product was treated with ether, and the clarified ethereal solution extracted with N-hydrochloric acid. The bases were recovered in the usual way and fractionally distilled. Methoxylepidine (6 g.) was recovered; the fraction (3·8 g.), b. p. 112—135°/0·25 mm., was dissolved in hot acetone (150 c.c.) and treated with a solution of picric acid (5 g.) in boiling acetone (100 c.c.). After half an hour the product was collected and recrystallised from acetone (about 1300 c.c.). Long yellow needles (5·35 g.) of the *picrate* of (VIII; R = Me) were thus obtained, m. p. 211—212° (decomp.) (Found: C, 53·3; H, 3·75. $C_{13}H_{13}ON,C_6H_3O_7N_3$ requires C, 53·3; H, 3·75%). The free base was an oil, b. p. 118—124°/0·25 mm. During this work the picrate of 6-methoxylepidine was prepared and found to have m. p. 232—233° (Pictet and Misner, *Ber.*, 1912, **45**, 1802, gave m. p. 223°).

6-*Methoxylepidine* N-*Oxide.*—6-Methoxylepidine (3·46 g.) in ethyl acetate (12 c.c.) was treated at − 5° with a solution (73 c.c.) of perbenzoic acid in ethyl acetate (14·6 g. in 350 c.c.). After 20 hours at 0° the crystalline *oxide benzoate* was collected (2·7 g.) and recrystallised from ethyl acetate; m. p. 127—128° (Found: C, 69·2; H, 5·4. $C_{11}H_{11}O_2N,C_7H_6O_2$ requires C, 69·4; H, 5·5%). On treatment with aqueous alkali the *oxide* separated; it was recovered with chloroform and crystallised from benzene, giving colourless needles, apparently hydrated, which subsided at 151—152° and became clear at 156—157° (Found: after drying at 60°: N, 7·5. $C_{11}H_{11}O_2N$ requires N, 7·4%). The *picrate* crystallised from alcohol in long yellow needles, m. p. 171—172° (Found: C, 49·0; H, 3·7. $C_{11}H_{11}O_2N,C_6H_3O_7N_3$ requires C, 48·8; H, 3·4%). The oxide was not reduced by sulphur dioxide in chloroform, or by hydrogen in the presence of palladised strontium carbonate, but gave methoxylepidine when kept overnight with zinc dust and acetic acid.

Oxidation of 6-*Methoxy*-4-*styrylquinoline.*—The base (0·9 g.) in chloroform (100 c.c.) was treated with a solution (25 c.c.) of perbenzoic acid in chloroform (15·7 g. in 300 c.c.). After 3 days at 0° oxidation was complete. The chloroform was washed with alkali, dried, and evaporated, and the residue crystallised from a little benzene, leaving the N-*oxide* in yellow crystals, m. p. 160—162° (Found: C, 77·5; H, 5·2. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4%). The *picrate* crystallised from ethyl acetate; m. p. 211° (Found: C, 57·4; H, 3·9; N, 11·4. $C_{18}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 56·9; H, 3·6; N, 11·1%).

Condensation of 6-*Methoxylepidine with Chloral.*—6-Methoxylepidine (27 g.), anhydrous chloral (27 g.), and dry pyridine (60 c.c.) were heated on the steam-bath for 7 hours. The mixture was poured into water, the solid collected, washed with alcohol, boiled with a little alcohol, cooled, collected and dried at 100° (34·2 g.). Recrystallisation from ethyl acetate gave 6-*methoxy*-4-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoline* (IX) in colourless needles, m. p. 195—196° (Found: C, 48·8; H, 4·1. $C_{12}H_{14}O_2NCl_3$ requires C, 48·4; H, 4·3%).

β-6-*Methoxy*-4-*quinolylacrylic Acid* (X).—The chloral compound (12 g.) was added to a boiling solution of potassium hydroxide (10·5 g.) in alcohol (50 c.c.) during ½ hour. After a further 2 hours' refluxing, water was added, and after treatment with charcoal the *acid* (X) was precipitated by acetic acid, collected, and dried (6·2 g.). Crystallisation from butanol gave pale yellow microscopic rods, m. p. 270° (decomp.) (Found: N, 6·1. $C_{13}H_{11}O_3N$ requires N, 5·8%).

6-*Methoxy*-4-*vinylquinoline Picrate.*—The acrylic acid (5 g.) in acetic acid–hydrobromic acid (30 c.c., saturated) was cooled to 0° and saturated with hydrogen bromide. After 2 days the mixture was

evaporated at low pressure. The residual crystalline cake, consisting essentially of the bromopropionic acid hydrobromide, was triturated with a little water, and the resulting suspension added gradually to a large excess of boiling saturated potassium carbonate solution covered with xylene. The mixture was boiled for an hour with one change of xylene. The united xylene extracts were washed with water, and the bases extracted with dilute sulphuric acid and passed into ether. The oil remaining after evaporation of the ether was converted into the *picrate* of (VIII; R = H), which crystallised from acetone in six-sided prisms or long needles, m. p. 210° (Found: C, 51·8; H, 3·4; N, 13·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4; N, 13·5%). The yield was poor.

Attempted Reaction of 6-*Methoxylepidine with Acetaldehyde.*—Lithium (1·72 g.) was cut up and stirred under nitrogen with ether (130 c.c.) during the addition of bromobenzene (20 g.). Next day 6-methoxylepidine (21·6 g.; freshly distilled) in ether was added, and then a solution of pure acetaldehyde in ether, until the red colour was discharged. After 20 minutes water (25 c.c.) and then hydrochloric acid (25 c.c.; *d* 1·19) were added, and the nitrogen stream stopped. The solid was collected, stirred with sodium carbonate solution, and extracted with chloroform; the chloroform solution was united with the ethereal filtrate. On removal of solvent the residue (27 g.) largely crystallised. Recrystallisation from light petroleum (b. p. 60—80°; charcoal) gave 6-methoxy-2-phenyl-4-methylquinoline in long colourless needles, m. p. 128° (John and Noziczka, *J. pr. Chem.*, 1925, **111**, 65, gave m. p. 129°) (Found: C, 82·1; H, 6·3. Calc. for $C_{17}H_{15}ON$: C, 81·9; H, 6·0%).

1-*Bromo*-2-*methoxy*-6-(2-*dibutylamino*-1-*hydroxyethyl*)*naphthalene Dipicrate.*—1-Bromo-2-methoxy-6-bromoacetylnaphthalene (7·16 g.; m. p. 127—130°) in dry ether (40 c.c.) was treated with dibutylamine (5·16 g.), and the mixture refluxed for 5 hours. The dibutylamine hydrobromide was removed, and the filtrate evaporated. The residue was reduced in the known manner with aluminium *iso*propoxide in *iso*propanol (35 c.c. of 3N); reduction was complete in 2 hours. The product was converted into the picrate, which gave after three crystallisations from alcohol orange rosettes (2·3 g.), yellow when powdered, of the *dipicrate* of (XII), m. p. 147—148° (Found: C, 45·6; H, 4·0; N, 10·9. $C_{21}H_{30}O_2NBr,2C_6H_3O_7N_3$ requires C, 45·7; H, 4·2; N, 11·4%).

Benzyl-n-*amylamine and* -*di*-n-*amylamine.*—Benzylamine (35·7 g.), *n*-amyl bromide (100 g.), and potassium hydroxide pellets (44 g.) were refluxed (bath 150°) for 10 hours. After cooling, water was added, and the oily layer dried over potassium hydroxide and potassium carbonate, and fractionated repeatedly at low pressure, giving (1) *benzyl*-n-*amylamine* (6 g.), b. p. 122—124°/10 mm. (Found: C, 81·5; H, 11·0; N, 7·8. $C_{12}H_{19}N$ requires C, 81·4; H, 10·7; N, 7·9%), *hydrochloride*, needles from acetone, m. p. 240° (Found: N, 6·8. $C_{12}H_{19}N,HCl$ requires N, 6·6%); and (2) *benzyldi*-n-*amylamine* (40·7 g.), b. p. 151—152°/10 mm. (Found: C, 82·8; H, 11·8; N, 5·5. $C_{17}H_{29}N$ requires C, 82·6; H, 11·7; N, 5·7%).

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