Reactions and Syntheses with Organometallic Compounds. Part 6.[1] A New Synthesis of Indole, Quinoline, and Benzazepine Derivatives *via* Arylnickel Complexes

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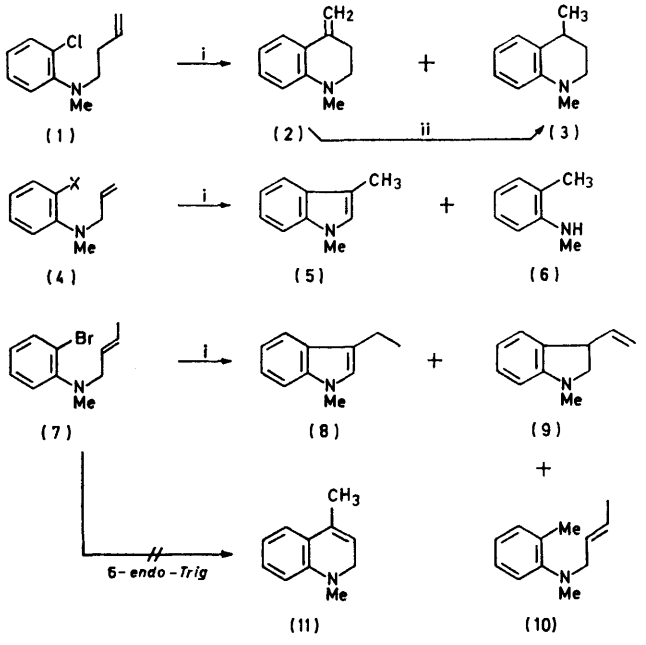
o-Chloroaniline derivatives with an internal double bond were treated with MeMgBr (200 mol %) in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ (1 mol %) to furnish heterocyclic compounds such as indole, quinoline, and even benzazepine derivatives in good yield.

WE have recently reported a new synthetic method for heterocyclic compounds, such as indoles, isoquinolines, and oxindoles, by use of arylpalladium [1] and arylnickel [2] complexes. For instance, *N*-allyl-*o*-chloro-*N*-methylaniline (4; X = Cl) reacted with a Grignard reagent (EtMgBr) in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ (1 mol %) to afford 1,3-dimethylindole although in poor yield.[2] This work revealed that the



SCHEME 1 Reagents: i, EtMgBr–1% $NiCl_2(PPh_3)_2$; ii, PtO_2–H_2

aryl halide could generally react with dialkyl [$RNiR(PPh_3)_2$] or zerovalent nickel [$Ni(PPh_3)_n$] complexes prepared *in situ* from the divalent nickel complex and Grignard reagent as above, to form initially an arylnickel complex, which was followed by cyclization of the internal double bond to produce the heterocyclic compound.

† The spectral data (n.m.r., mass, i.r., and u.v.) of compound (3) and elemental analysis of the picrate supported this structure, but the m.p. (121—123°) of the picrate did not agree with that previously reported [picrate, m.p. 175° J. Metzer, H. Larive, E-J. Vincent, and R. Dennilaure, *Bull. Soc. chim. France*, 1967, 46]. When *N*-methyl-lepidine was reduced with platinum oxide in ethanol, there was obtained 1,4-dimethyl-1,2,3,4-tetrahydroquinoline which formed a picrate, m.p. 119—121°, which was shown to be identical with the above picrate by mixed m.p. (119—122°) determination.

In this paper, we describe the applicability of this type of cyclization using arylnickel complexes. When compound (1) was treated with EtMgBr and a catalytic amount of $NiCl_2(PPh_3)_2$, 1,4-dimethyl-1,2,3,4-tetrahydroquinoline (3) was obtained, but the yield was very poor (8.7%). Use of MeMgBr instead of EtMgBr in the above procedure, however, proved to be much more effective, giving 1-methyl-4-methylene-1,2,3,4-tetrahydroquinoline (2) in 90.4% yield. Compound (2) was readily hydrogenated with Adams' catalyst in ethanol to furnish 1,4-dimethyl-1,2,3,4-tetrahydroquinoline (3).† In the same manner, compound (4) gave 1,3-dimethylindole (5) in fairly good yield (53.4%) along with *o*,*N*-dimethylaniline (6) (11.7%). In this case, compounds not involving a five-membered ring were not detected. Similarly, compound (7) gave 1-methyl-3-ethylindole (8) and 1-methyl-3-vinylindoline (9) in 23.6 and 15.7% yields, respectively, but 1,4-dimethyl-1,2-dihydroquinoline (11) could not be detected. It should be pointed out in this reaction that 5-*exo*-*Trig* cyclization occurs preferentially rather than 6-*endo*-*Trig* closure,[3] although compound (7) can generate both five- and six-membered rings.

Reaction of the compound (1) with various Grignard reagents in the presence of $NiCl_2(PPh_3)_2$

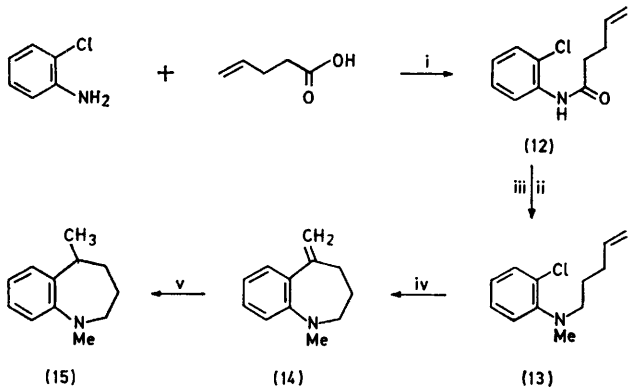
Run	RMgBr	Solvent	Product (%) (2)	(3)	(1)
1	EtMgBr	Ether	0	8.7	40.0
2	PhMgBr	THF	34.0	0	0
3	MeMgBr	THF	90.4	0	0

Recently, a mechanism for cyclization of aryl radicals containing unsaturated *ortho*-substituents was proposed by Beckwith *et al.*, who claimed that aryl radicals generated by interaction of tributylstannane with aryl iodides cyclize regiospecifically to afford the newly formed radical centre exocyclic to the newly formed ring.[4] They also revealed that *N*-allyl-*o*-iodo-*N*-methylaniline (4; X = I) reacted with tributylstannane and azobisisobutyronitrile to give 1,3-dimethylindoline as the sole cyclized product involving a five-membered ring. On these reactions, 5-*exo*-*Trig* closures are preferred to 6-*endo*-*Trig* cyclizations. It seems significant that these results are in agreement with ours.

Thus, the extension of our method to synthesis of a compound containing a seven-membered ring was attempted, since it was interesting not only for establishing the effectiveness of the method, but also for investig-

ation of cyclization modes. For the synthesis of the starting material (13), *o*-chloroaniline was condensed with allylacetic acid in the presence of $ClCO_2Et$ and NEt_3 to give (12), which was methylated with NaH and MeI in tetrahydrofuran and reduced with $LiAlH_4$ in ether to afford (13). A mixture of (13), MeMgBr, and $NiCl_2(PPh_3)_2$ (1 mol %) in tetrahydrofuran was refluxed to give the expected 1-methyl-5-methylene-2,3,4,5-tetrahydro-1*H*-benzazepine (14), but the yield was rather low (22.7%). However, when additional $NiCl_2(PPh_3)_2$ (3 mol %) was added to the above mixture, the yield of the cyclized product (14) was raised to 62.0%. 7-*exo-Trig* closure by this method was thus successfully effected. Compound (14) was hydrogenated with platinum oxide in ethanol to afford 1,5-dimethyl-2,3,4,5-tetrahydro-1*H*-benzazepine (15).

The reactions can be assumed to proceed through the general pathway shown in Scheme 3. The dialkylnickel complex ($R^3NiR^3L_2$) was generated from reaction



SCHEME 2 Reagents: i, ClCOOEt–NEt_3; ii, MeI–NaH; iii, $LiAlH_4$–Et_2O; iv, MeMgBr–3% $NiCl_2(PPh_3)_2$; v, PtO_2–H_2

of a Grignard reagent (R^3MgBr) with $NiCl_2(PPh_3)_2$ and was then inserted to furnish the arylnickel complex (17), which reacted with an internal double bond to form the alkynickel complex (18). The hydridonickel complex ($HNiXL_2$) can be eliminated from (18) to provide the cyclic product (23). On the other hand, the dialkylnickel complex (20) formed by attack of the Grignard reagent on (18), underwent reductive elimination to generate a zerovalent nickel complex (NiL_n), which gave the saturated cyclic compound (22).* Alternatively, compound (21; $R^1 = R^2 = R^{3'} = Me$, $n = 1$), = (10), can be obtained as the cross-coupling product of the reaction of the aryl halide (16) with Grignard reagent (R^3MgBr); a similar reaction has been reported by Kumada *et al.*[5] The hydridonickel complex ($HNiXL_2$) should presumably be converted by Grignard reagent into alkylhydridonickel complex ($HNiR^1L_2$) or zerovalent nickel complex (NiL_n), which might react with (16) to give (17) which then reacts as before.

These results suggest that various heterocyclic compounds can be obtained by this simple method. Further studies are in progress.

* When EtMgBr(R^3MgBr in Scheme 3) was used as a Grignard reagent, 1,4-dimethyl-1,2,3,4-tetrahydroquinoline [(3) ≡ (2); $R^1 = Me$, $R^2 = R^{3'} = H$, $n = 2$)] was obtained, which suggested that ethylene was eliminated from ethylnickel complex (20; $R^3 \equiv Et$).[2a]

EXPERIMENTAL

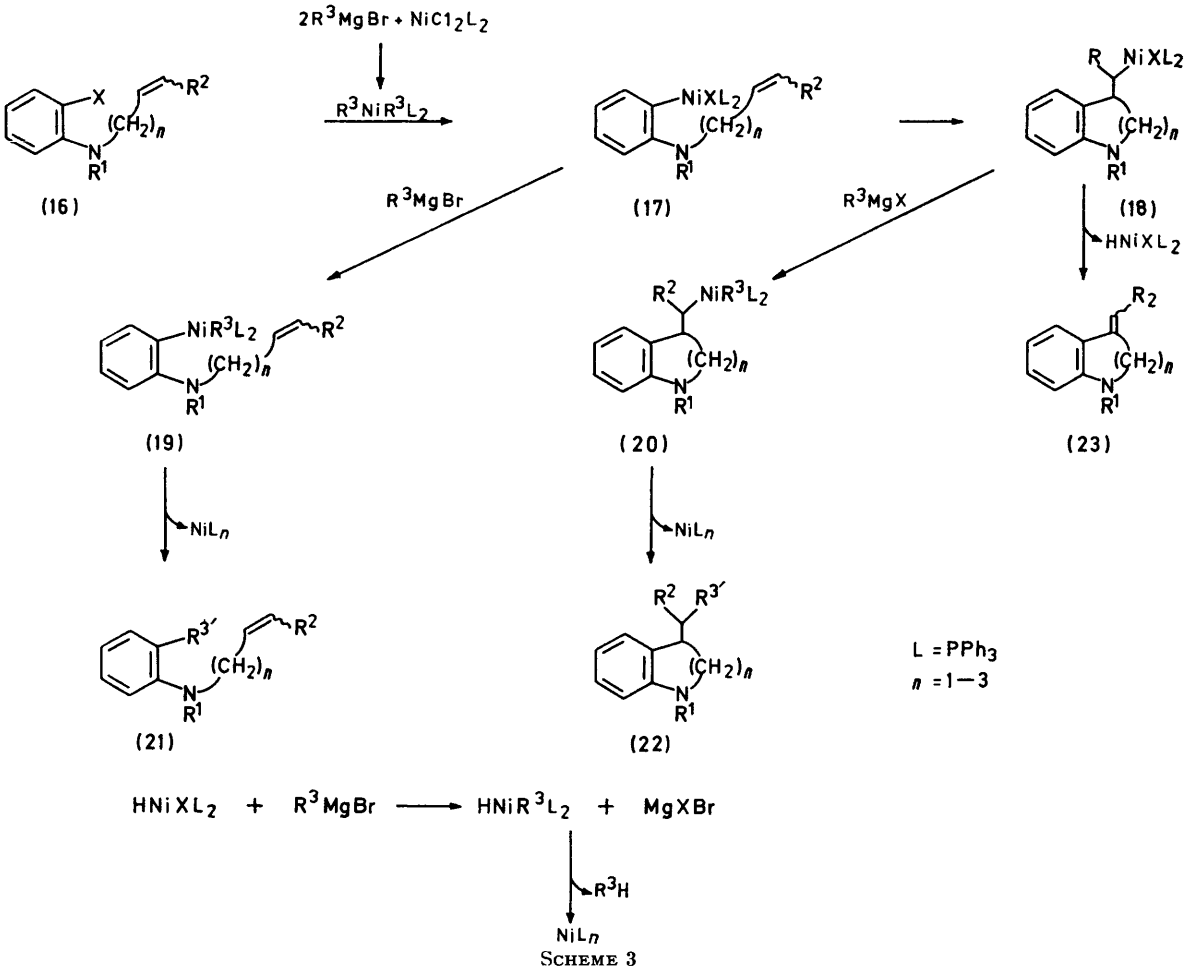
M.p.s were measured with a hot stage microscope (Yanaco MP-J2) and with a m.p. apparatus, and are uncorrected. Spectra were measured on a JASCO IRA-2 diffraction grating i.r. spectrophotometer and a Hitachi RMU-7M double focusing mass spectrometer. *N*-Allyl-*o*-chloro-*N*-methyl- and *N*-but-3-enyl-*o*-chloro-*N*-methylaniline were prepared by a similar method to those previously described.[4] Methylmagnesium bromide solution was commercially available (*ca.* 1M in tetrahydrofuran; Tokyo Kasei Kogyo). Solvents were purified by established procedures.

o-*Chloro*-N-*methyl*-N-*pent*-4-*enylaniline* (13).—Ethyl chloroformate (1.04 g, 7.98 mmol) in tetrahydrofuran (5 ml) was added to a solution of allylacetic acid (0.91 g, 9.1 mmol) and NEt_3 (1.08 g, 8.36 mmol) in tetrahydrofuran (25 ml) at −12 to −15° on ice–salt cooling. After 10 min, *o*-chloroaniline (0.97 g, 7.6 mmol) in tetrahydrofuran (5 ml) was added to the mixture at the same temperature, and the whole stirred at room temperature overnight. Solid was filtered off and solvent removed. The residue was dissolved in ether, and the ether layer was washed with 10% HCl and dried (Na_2SO_4). The solvent was removed and the residue was recrystallized from ethyl acetate, acetone, and ether to give of *N*-(*o*-chlorophenyl)allylacetamide (12) (1.13 g, 71.0%), $\nu_{max.}$ 3 260 and 1 650 cm^{-1}. To the suspension of NaH (340 mg, 8.5 mmol; 60% in mineral oil) in tetrahydrofuran (10 ml) was added amide (12) (1.187 g, 5.67 mmol) under a stream of nitrogen. After evolution of hydrogen ceased, MeI (1.16 g, 11.3 mmol) was added and the mixture was stirred for 1.5 h at room temperature. Water was added and the aqueous solution was extracted with benzene. The organic layer was dried (Na_2SO_4) and evaporated. Chromatography on silica gel eluting with acetone–hexane (1 : 6) afforded oily *N*-(*o*-chlorophenyl)-*N*-methylallylacetamide (13) (0.820 g, 64.7%), $\nu_{max.}$ 1 680 cm^{-1}. *N*-(*o*-Chlorophenyl)-*N*-methylallylacetamide (840 mg, 3.77 mmol) in ether (10 ml) was added to a suspension of $LiAlH_4$ (286 mg, 7.53 mmol) in ether (10 ml) with ice cooling and the mixture was stirred at room temperature for 1 h. After water was carefully added, the solid was filtered and washed with ether. The combined ether layers were extracted with 10% HCl and the acidic layer was neutralized with K_2CO_3 and extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on silica gel eluting with hexane–acetone (6 : 1) to give *o*-chloro-*N*-methyl-*N*-pent-4-enylaniline (13) (416.7 mg, 53.1%), oil, *m/e* 209 and 211 (M^+); δ($CDCl_3$) 0.45—1.8 (2 H, m), 2.72 (3 H, s, NCH_3), 3.0 (2 H, m), 4.76br (1 H, s, =CH), 5.05br (1 H, d, =CH), 5.50—6.17 (1 H, m, −CH=), and 6.65—7.45 (4 H, m, ArH).

General Procedure.—A solution of MeMgBr (*ca.* 1 mol in tetrahydrofuran; 2 equiv.) was added to the solution of *o*-halogenoaniline derivative (1 equiv.) and a catalytic amount of $NiCl_2(PPh_3)_2$ (0.01 equiv.) in tetrahydrofuran under nitrogen with ice cooling. The mixture was stirred at room temperature for 30 min, refluxed for 30—45 min, saturated NH_4Cl solution was added with ice cooling, and the mixture was extracted with ether. The ether layer was purified by an appropriate method.

1-*Methyl*-4-*methylene*-1,2,3,4-*tetrahydroquinoline* (2). A solution of MeMgBr (7.4 mmol) was added to a solution of

N-but-3-enyl-*o*-chloro-N-methylaniline (1) (730 mg, 3.7 mmol) and $NiCl_2(PPh_3)_2$ (24 mg, 0.037 mmol) in tetrahydrofuran (5 ml). After the usual work, the basic product was purified by chromatography on silica gel eluting with ether–hexane (4 : 96) to give (2), an oil which gradually darkened on standing, *m/e* 159 (M^+) and 144 ($M^+ - CH_3$); $\nu_{max.}$ 1 625 and 1 600 cm^{-1}; $\delta(CCl_4)$ 2.60 (2 H, m, NCH_2), 2.80 (3 H, s, NCH_3), 3.15 (2 H, m), 4.69br (1 H, s, =CH), 5.31br (1 H, s, =CH), and 6.4—7.5 (4 H, m, ArH).



SCHEME 3

1,4-*Dimethyl*-1,2,3,4-*tetrahydroquinoline* (3). The solution of 1-methyl-4-methylene-1,2,3,4-tetrahydroquinoline (2) (172 mg) in ethanol (10 ml) containing PtO_2 (8 mg) was hydrogenated at atmospheric pressure at room temperature. The catalyst was filtered off and ethanol was removed. Chromatography on silica gel of the residual oil gave (3) (149 mg; 85.6%), oil, *m/e* 161 (M^+) and 146 ($M^+ - CH_3$); $\nu_{max.}$ 1 600 cm^{-1}; $\delta(CCl_4)$ 1.22 (3 H, d, *J* 7 Hz, CH_3), 1.55—2.3 (3 H, m), 2.85 (3 H, s, NCH_3), and 6.52—7.3 (4 H, m, ArH); *picrate* m.p. 121—123° (from ethanol) (Found: C, 52.45; H, 4.6; N, 14.2. $C_{17}H_{18}N_4O_7$ requires C, 52.3; H, 4.65; N, 14.35%).

1,3-*Dimethylindole* (5). A solution of MeMgBr (7.1 mmol) was added to a solution of *N*-allyl-*o*-bromo-*N*-methylaniline (4; X = Br) (800 mg, 3.54 mmol) and $NiCl_2(PPh_3)_2$ (22 mg, 0.035 mmol) in tetrahydrofuran (5 ml). After the usual work, the neutral product was purified by chromatography on silica gel eluting with ether–hexane (4 : 96) to give an oil (272 mg, 53.0%) whose spectral data were identical with those of 1,3-dimethylindole,[6] *m/e* 145 (M^+); $\nu_{max.}$ 1 610 cm^{-1}; $\delta(CCl_4)$ 2.20 (3 H, s, CH_3), 3.75 (3 H, s, NCH_3), 6.40br (1 H, s, 2-H), and 7.0—7.5 (4 H, m, ArH). The acidic layer was neutralized with K_2CO_3 and extracted with ether to give *o*,*N*-dimethylaniline (6) (49.9 mg, 11.7%).[7]

Reaction of o-*Bromo*-N-*methylallyl*-N-*methylaniline* (7) *with* MeMgBr *and a Catalytic Amount of* $NiCl_2(PPh_3)_2$.—A solution of MeMgBr (4 mmol) was added to a solution of *o*-bromo-*N*-methylallyl-*N*-methylaniline (7) (480 mg, 2 mmol) and $NiCl_2(PPh_3)_2$ (13 mg, 0.02 mmol). After the usual work-up, the organic layer was treated with 10% HCl, dried (Na_2SO_4), and the solvent was removed. The residual oil was purified by chromatography on silica gel eluting with ether–hexane (4 : 96) to give 3-ethyl-1-methylindole (8) [8] (75 mg, 23.6%), oil, *m/e* 159 (M^+) and 144 ($M^+ - CH_3$); $\nu_{max.}$ 1 620 cm^{-1}; $\delta(CCl_4)$ 1.25 (3 H, t, *J* 7 Hz, CH_3), 2.68 (2 H, q, *J* 7 Hz, CH_2), 3.50 (3 H, s, NCH_3), 6.53 (1 H, s, 2-H), and 6.75—7.5 (4 H, m, ArH). The acidic solution was neutralized with K_2CO_3 and extracted with ether. The ether layer was dried over Na_2SO_4 and the ether was removed. The residual oil was purified by chromatography on silica gel eluted with ether–hexane (4 : 96). The first fraction gave *o*,*N*-dimethyl-*N*-methylallylaniline (10) (78.5 mg, 22.4%), oil, $\nu_{max.}$ 1 600 cm^{-1}; $\delta(CCl_4)$ 1.70br (3 H, d, CH_3), 2.29 (3 H, s, CH_3), 2.60 (3 H, s, NCH_3), 3.36 (2 H, m,

CH_2), 5.55 (2 H, m, $-CH=CH-$), and 6.7—7.2 (4 H, m, ArH). The second fraction gave 1-methyl-3-vinylindoline (9) (49.9 mg, 15.7%), oil, *m/e* 159 (M^+), 132, and 117; $\nu_{max.}$ 1 630 and 1 600 cm^{-1}; $\delta(CCl_4)$ 2.70 (3 H, s, NCH_3), 2.9—4.0 (3 H, m, NCH_2), 4.9—5.9 (3 H, m, $CH=CH_2$), and 6.3—7.1 (4 H, m, ArH).

1-*Methyl*-5-*methylene*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* (14).—A solution of MeMgBr (2.9 mmol) was added to a solution of *o*-chloro[*N*-methyl-*N*-pent-4-enylaniline (13) (300 mg, 1.43 mmol) and $NiCl_2(PPh_3)_2$ (28.2 mg, 0.043 mmol) in tetrahydrofuran (6 ml). The solution was refluxed for 6.5 h and the mixture was treated as usual. The basic product was purified by preparative chromatography on silica gel eluting with hexane–benzene (1 : 1) to give (14) (155.2 mg, 62%), oil, *m/e* 173 (M^+) and 158 ($M^+ - CH_3$), $\nu_{max.}$ 1 620 and 1 595 cm^{-1}; $\delta(CCl_4)$ 2.94 (3 H, s, NCH_3), 4.97br (1 H, s, =CH), 5.23 (1 H, d, *J* 2 Hz, =CH), and 6.6—7.4 (4 H, m, ArH), *picrate*, m.p. 121—122° (from ethanol) (Found: C, 53.6; H, 4.4; N, 13.85%. $C_{18}H_{18}N_4O_7$ requires C, 53.75; H, 4.5; N, 13.9%).

1,5-*Dimethyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* (15).—The solution of 1-methyl-5-methylene-2,3,4,5-tetrahydro-1*H*-1-benzazepine (14) (90 mg) in ethanol (10 ml) containing PtO_2 (5 mg) was hydrogenated at atmospheric pressure at room temperature. The catalyst was filtered off and the solvent was removed under reduced pressure. The residual oil was purified by preparative chromatography on silica gel eluting with hexane–benzene (1 : 1) to give 1,5-dimethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (15) (80.6 mg, 88.7%), oil, $\nu_{max.}$ 1 600 cm^{-1}; $\delta(CCl_4)$ 1.32 (3 H, d, *J* 7 Hz, CH_3), 2.85 (3 H, s, NCH_3), and 6.8—7.4 (4 H, m, ArH), *picrate*, m.p. 152—154° (from ethanol) (Found: C, 53.5; H, 4.95; N, 13.85. $C_{18}H_{20}N_4O_7$ requires C, 53.45; H, 5.0; N, 13.85%).

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