84. *Attempts to extend the Mannich Reaction to Derivatives of 4-Methylquinoline and 2 : 4-Dinitrotoluene.*

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2 : 6-*Dimethoxy*-4-*methylquinoline*, when treated with formaldehyde and piperidine under a variety of conditions, gave, not the expected 2 : 6-dimethoxy-4-piperidylethylquinoline (cf. Kermack and Muir, J., 1931, 3089), but a product, $C_{11}H_{11}O_2N$, m. p. 271°, which was also obtained (a) in this reaction in the presence of only a trace of piperidine and (b) when 2 : 6-*dimethoxy*- or 6-*methoxy*-2-*ethoxy*-4-*methylquinoline* was boiled with dilute hydrochloric acid so that methoxyl or ethoxyl in the 2-position was converted into hydroxyl. Comparison of 2-hydroxy-6-methoxy-4-methylquinoline (m. p. 255°) and the new compound (see p. 301) and the m. p.'s of mixtures of the compounds themselves (245—250°) and of the picrates (145—155°) indicate that the two are distinct. All attempts to convert the compound of m. p. 271° into that of m. p. 255° by boiling with water, acid, or alkali have failed : the former may be the ketamic form, and the latter the enimic form, but, if so, the stability to acid and alkali is difficult to explain. No new product was obtained when 8-chloro-2-methoxy-4-methylquinoline was condensed with formaldehyde and piperidine under various conditions.

When 2 : 4-dinitrotoluene was treated with formaldehyde and piperidine (2 mols. of each) in the presence of alcohol *αγ-dipiperidino*-β-(2 : 4-*dinitrophenyl*)*propane*, $(C_5H_{10}N\cdot CH_2)_2CH\cdot C_6H_3(NO_2)_2$ (I), was obtained, but with only 1 mol. of each (I) was produced in small quantity together with α-piperidino-β-(2 : 4-dinitrophenyl)ethane, $C_5H_{10}N\cdot CH_2\cdot CH_2\cdot C_6H_3(NO_2)_2$. From 2 : 4-dinitrotoluene, formaldehyde, and diethylamine, the only new product isolated was an oily base, α-diethylamino-β-(2 : 4-dinitrophenyl)-ethane : even with excess of formaldehyde and diethylamine, αγ-bisdiethylamino-β-(2 : 4-dinitrophenyl)propane does not appear to be formed. These experiments show that the Mannich reaction takes place with 2 : 4-dinitrotoluene, though similar experiments with *o*-nitrotoluene were unsuccessful (cf. Kermack and Muir, *loc. cit.*).

EXPERIMENTAL.

2 : 6-*Dimethoxy*-4-*methylquinoline*.—2-Chloro-6-methoxy-4-methylquinoline (8 g.) was refluxed with NaOMe (6 g. Na in 60 c.c. MeOH) for 2 hr., the excess of MeOH distilled off, and the deep red liquid poured into H_2O (150 c.c.); the 2 : 6-*dimethoxy*-4-*methylquinoline* obtained, recryst. from light petroleum (b. p. 40—60°), formed long, thick, white, rectangular prisms (7·5 g.), m. p. 56° (Found : N, 7·0. $C_{12}H_{13}O_2N$ requires N, 6·9%). Hydrochloride, white cryst. solid, m. p. 237° (decomp.).

6-*Methoxy*-2-*ethoxy*-4-*methylquinoline*, similarly prepared, formed small rectangular prisms, m. p. 81°, from aq. EtOH (Found : N, 6·6. $C_{13}H_{15}O_2N$ requires N, 6·5%).

6-*Methoxy*-2-*piperidino*-4-*methylquinoline*, obtained by refluxing 2-chloro-6-methoxy-4-methylquinoline (2 g.) and piperidine (5 c.c.) for 4 hr. and pouring the cooled product into H_2O (100 c.c.), crystallised from light petroleum in thick colourless plates (1·5 g.), m. p. 97° (Found : N, 10·9. $C_{16}H_{20}ON_2$ requires N, 10·9%). The hydrochloride rapidly absorbs moisture from the air and the picrate is a pale yellow cryst. powder, m. p. 135°.

6-*Methoxy*-2-*piperazino*-4-*methylquinoline*, similarly obtained from 2-chloro-6-methoxy-4-methylquinoline (1 g.) and piperazine hydrate (6 g.) at 140° (5 hr.), separated from hot H_2O as a colourless oil which slowly formed microscopic prisms, m. p. 92° (Found : N, 16·1. $C_{15}H_{19}ON_3$ requires N, 16·3%).

8-*Chloro*-2-*hydroxy*-4-*methylquinoline*.—(a) *o*-Chloroacetoacetanilide (10 g.), dissolved in paraffin oil (40 c.c.), was rapidly heated to 240°, and cooled after 5 min.; 8-*chloro*-2-*hydroxy*-4-*methylquinoline* separated as a white cryst. solid mixed with a little tar. (b) *o*-Chloroacetoacetanilide (14 g.) was heated for 4 hr. at 65° with conc. H_2SO_4 (6 c.c.), and the cooled solution added to H_2O (100 c.c.). Both specimens crystallised from EtOH in needles, m. p. 230°. Yield, (a) 4·5 g., (b) 8·5 g. (Found : N, 7·4. $C_{10}H_8ONCl$ requires N, 7·2%). The substance gave no colour with alc. $FeCl_3$.

2 : 8-*Dichloro*-4-*methylquinoline* was prepared from 8-chloro-2-hydroxy-4-methylquinoline (8 g.), $POCl_3$ (6 c.c.), and PCl_5 (8 g.), the mixture being finally heated for 2 hr. at 130—140° and poured on ice; it crystallised from light petroleum in long rectangular prisms (7 g.), m. p. 87—88° (Found : N, 6·9. $C_{10}H_7NCl_2$ requires N, 6·6%).

8-*Chloro*-2-*methoxy*-4-*methylquinoline*, obtained from 2 : 8-dichloro-4-methylquinoline (4 g.) and NaOMe (2 g. Na in 20 c.c. MeOH; 2 hrs.' heating), crystallised from ligroin (charcoal) in thick, white, rectangular prisms (2·8 g.), m. p. 122° (Found : N, 6·9. $C_{11}H_{10}ONCl$ requires N, 6·7%).

8-*Chloro*-2-*piperidino*-4-*methylquinoline*, prepared from 2 : 8-dichloro-4-methylquinoline (2 g.) and piperidine (10 c.c.), crystallised from EtOH in pinkish-white, flat, flaky crystals (1 g.), m. p. 125—126° (Found : N, 10·9. $C_{15}H_{17}N_2Cl$ requires N, 10·8%). Picrate, m. p. 159°.

8-*Chloro*-2-*piperazino*-4-*methylquinoline* crystallised from H_2O in white radial needles, m. p. 135° (Found : N, 15·7. $C_{14}H_{16}N_3Cl$ requires N, 16·1%).

Preparation of the Compound, m. p. 271°.—(1) 2 : 6-Dimethoxy-4-methylquinoline (2·4 g.; 0·1 mol.), CH_2O (1·5 c.c. of 40% solution; 0·2 mol.), and a trace of piperidine hydrochloride were refluxed for 8 hr., a white solid slowly separating. (2) 2 : 6-Dimethoxy-4-methylquinoline or 6-methoxy-2-ethoxy-4-methylquinoline (1 g.) was boiled with *N*-HCl (10 c.c.) for 4 hr. Each solution was basified with K_2CO_3, and the unchanged base removed by steam distillation. The *compound* crystallised from H_2O in white radial needles, m. p. and mixed m. p. 271° (Found : C, 69·8; H, 5·9; N, 7·2. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8; N, 7·4%).

The compound, m. p. 271°, is insol. in cold dil. or conc. HCl or cold dil. NaOH aq., sol. in hot conc. HCl, partly sol. in hot dil. HCl or dil. NaOH aq., separating unchanged on cooling; gives with hot alc. $FeCl_3$ a light red colour which fades on cooling; forms a picrate, m. p. 165—166°, crystallising in long yellow needles; and is converted by conc. H_2SO_4 into a compound which contains N but no S and crystallises from H_2O in long needles blackening at about 290° but unmolten at 310°.

2-Hydroxy-6-methoxy-4-methylquinoline, m. p. 255°, forms long needles, is insol. in cold dil. HCl, sol. in hot dil. HCl, cold or hot conc. HCl, and cold dil. NaOH aq., is unchanged by conc. H_2SO_4, gives a deep red colour with alc. $FeCl_3$, and yields a picrate, m. p. 191°, crystallising in small yellow prisms.

αγ-Dipiperidino-β-(2 : 4-dinitrophenyl)propane.—2 : 4-Dinitrotoluene (9·1 g.; 0·05 mol.), CH_2O (7·5 c.c. of 40% solution; 0·1 mol.), and piperidine (8·5 g.; 0·1 mol.) were heated with sufficient EtOH for 2 hr., the deep red solution was poured into H_2O (150 c.c.), and the white cryst. ppt. obtained was filtered off, dissolved in dil. HCl, filtered, and basified with NH_3 aq. The *αγ-dipiperidino-β-(2 : 4-dinitrophenyl)propane* obtained, recryst. from EtOH, formed long hexagonal needles (15 g.), m. p. 134° (Found: C, 60·5; H, 7·4. $C_{19}H_{28}O_4N_4$ requires C, 60·6; H, 7·5%). Picrate, m. p. 191°.

α-Piperidino-β-(2 : 4-dinitrophenyl)ethane.—CH_2O (3·5 c.c. of 40% solution; 0·05 mol.) and piperidine (4·25 g.; 0·05 mol.) were mixed together, and 2 : 4-dinitrotoluene (9·1 g.) added together with sufficient EtOH to form a homogeneous solution, which was heated on the water-bath for 4 hr. On cooling, crystals of αγ-dipiperidino-β-(2 : 4-dinitrophenyl)propane separated and were removed. The filtrate was poured into H_2O, and the oil which separated was dissolved in dil. HCl (charcoal), repptd. by NH_3 aq., and converted into *α-piperidino-β-(2 : 4-dinitrophenyl)ethane picrate*, m. p. 175° after recrystn. from C_6H_6 (Found: N, 16·3. $C_{13}H_{17}O_4N_3,C_6H_3O_7N_3$ requires N, 16·5%).

α-Diethylamino-β-(2 : 4-dinitrophenyl)ethane picrate, similarly obtained from CH_2O (3·75 c.c. of 40% solution; 0·1 mol.), $NHEt_2$ (3·65 g.; 0·1 mol.), and 2 : 4-dinitrotoluene (9·1 g.; 0·1 mol.) in EtOH, had m. p. 129—130° after recrystn. from C_6H_6 (Found: C, 43·3; H, 3·7; N, 17·1. $C_{12}H_{17}O_4N_3,C_6H_3O_7N_3$ requires C, 43·5; H, 4·0; N, 16·9%).

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