5. *A New Chromone Synthesis.*

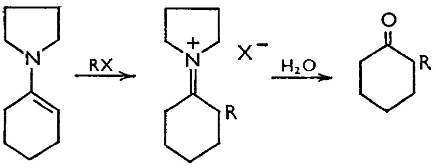
By B. B. Millward.

Reduction of *NN*-dimethylaniline and of *NN*-dimethyl-*p*-toluidine by sodium and alcohol in liquid ammonia afford the 2,3-dihydro-amines as main products. 2,3-Dihydro-*NN*-dimethyl-*p*-toluidine (II) gives 7,8-dihydro-2,6-dimethylchromone (IV) with diketen.

The " enamines," $R_2N{\cdot}C{:}C$, have been rather neglected since the observation [1] that ethyl β-diethylaminocrotonate added methyl iodide in a 1,3-manner:

$$EtO_2C{\cdot}CH{:}CMe{\cdot}NEt_2 \xrightarrow{MeI} EtO_2C{\cdot}CHMe{\cdot}CMe{:}\overset{+}{N}Et_2\ I^- \xrightarrow{H_2O} EtO_2C{\cdot}CHMe{\cdot}CO{\cdot}Me$$

Similar alkylations and acetylations by a variety of electrophilic reagents (RX) have been reported,[2,3] the cyclohexeneamine (I) being used, prepared from pyrrolidine and cyclohexanone.



(I)

It was hoped that addition of diketen to 2,3-dihydro-*NN*-dimethyl-*p*-toluidine (II) would give an intermediate (III) suitable for steroid syntheses. Instead, the product proved to be 7,8-dihydro-2,6-dimethylchromone (IV).

The need to prepare the conjugated dienamine (II) afforded an opportunity to examine in greater detail the reductions of *NN*-dimethylaniline and of *NN*-dimethyl-*p*-toluidine

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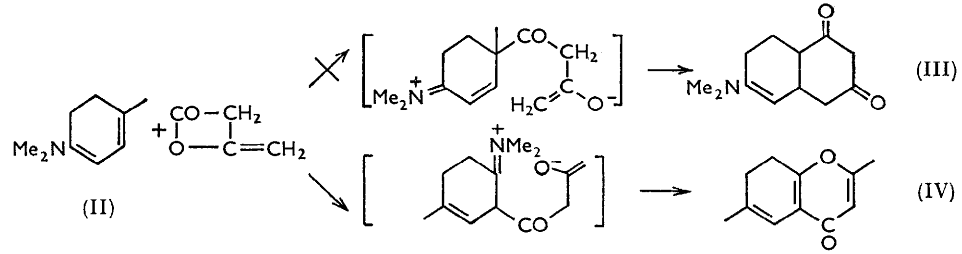
[1] Robinson, *J.*, 1916, **109**, 1038.

[2] Stork, Terrell, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1954, **76**, 2029.

[3] Stork and Landesman, *ibid.*, 1956, **78**, 5128.

described by Birch.[4] The dihydro-compounds he obtained were hydrolysed directly to cyclohexanones. Unexpectedly, the main products are the 2,3-dihydro-amines rather than the 2,5-dihydro-amines.



The first experiments on dimethylaniline showed that the products were similar whether the sodium ethoxide by-product was filtered off from the reaction mixture or washed out with water before distillation. However, the more convenient water-wash did lead to a little hydrolysis. The aromatic amines had absorption bands near 2520 Å whereas the dihydro-amines showed minimal absorption near this wavelength, so enabling the extent of reduction to be estimated spectroscopically. The product from these reductions had a band ($\lambda_{max.}$ 3030 Å, ε 7400) which must have been due to 2,3-dihydrodimethylaniline. The conjugation of a double bond with an amino-group results in light absorption similar to that of a conjugated diene,[5] and 1-diethylaminobuta-1,3-diene absorbs at $\lambda_{max.}$ 2810 Å (ε 23,500). Comparison with 2,3-dihydro-*NN*-dimethyl-*p*-toluidine (II; $\lambda_{max.}$ 3010 Å, ε 10,500) indicated that the total reduction product contained about 75% of the 2,3-dihydro-compound (II). Hydrolysis with aqueous oxalic acid was too vigorous, the resulting cyclohex-3-enone containing roughly 10% of cyclohex-2-enone because of rearrangement.

Closer attention was paid to the reduction of *NN*-dimethyl-*p*-toluidine. The rapid method [7] using lithium gave a similar product to that from Birch's reduction, but reduction was incomplete at the concentrations used. Substantially pure 2,3-dihydro-*NN*-dimethyl-*p*-toluidine (II) was isolated by fractional distillation of the product from a large-scale reduction by Birch's method, and treatment of a solution of this enamine in light petroleum with oxalic acid solution gave an excellent yield of 4-methylcyclohex-3-enone (V). This is a useful synthesis for pure cyclohex-3-enones.[4] Treatment of the enamine (II) with a catalytic quantity of potassium amide in liquid ammonia, followed by decomposition with ethanol, regenerated the starting material (~91%) and some 3,4,5,6-tetrahydro-amine (~9%) due to incidental reduction.

Fractionation of the lower-boiling components of the reduction product did not provide a fraction free from the diene (II) or ketones. Fraction B was largely the 3,4,5,6-tetrahydro-amine since hydrolysis gave 4-methylcyclohexanone. Hydrolysis of the next fraction, C, in which the light absorption showed at most 9% of the conjugated diene, gave 4-methylcyclohexanone and 4-methylcyclohex-3-enone (19%), as judged from hydrogenation data. Thus the fraction contained the 2,3-dihydro-amine (II; 9%), the 2,5-dihydro-amine (VI; 10%), and the 3,4,5,6-tetrahydro-amine (81%).

It appears that in reduction by Birch's method of *NN*-dimethyl-*p*-toluidine, 2,3-dihydro-*NN*-dimethyl-*p*-toluidine (II) is the main product (75%) with smaller amounts of the 2,5-isomer (VI) and the 3,4,5,6-tetrahydro-amine. The primary product is probably the 2,5-dihydro-compound which largely isomerises *via* the intermediate (VII) to the diene (II), some of which undergoes further reduction.[6]

An exothermic reaction ensued when 2,3-dihydro-*NN*-dimethyl-*p*-toluidine (II) was

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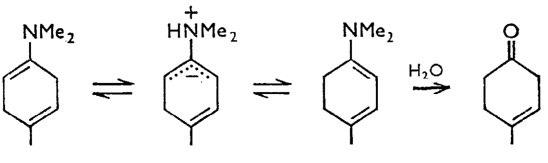
[4] Birch, *J.*, 1946, 593.
[5] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45.
[6] Birch and Smith, *Quart. Reviews*, 1958, **12**, 17.
[7] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5361.

mixed with diketen in ether, and from the product 7,8-dihydro-2,6-dimethylchromone (IV; 24%) was separated. The structure was established by quantitative hydrogenation of the 5,6-double bond, and by dehydrogenation to 2,6-dimethylchromone, identical with a sample synthesised from *p*-cresol and tetrolic ester. Generally, catalytic hydrogenation of chromones effects preferential reduction of the heterocyclic ring with the formation of chromans,[8] and it seems that chromones with partially reduced carbocyclic rings are new. The reaction of enamines with diketen may also serve as a synthesis of 2-methyl-1,4-pyrones and related compounds.



(VI) (VII) (II) (V)

EXPERIMENTAL

M. p.s were observed on a Kofler block. Ultraviolet absorption spectra of cyclohexane solutions were determined in a Unicam SP.500 spectrophotometer, and infrared spectra of carbon disulphide solutions were measured by means of a Perkin–Elmer model 21 double-beam instrument. " Light petroleum " refers to the fraction, b. p. 30—40°. All solvents were anhydrous, and the reduction products were handled under dry nitrogen.

The aromatic amines were distilled from toluene-*p*-sulphonyl chloride and then fractionally distilled *in vacuo*: dimethylaniline had b. p. 42°/0·3 mm., n_D^{20} 1·5584, $\lambda_{max.}$ 2515 and 2965 Å (ε 18,000 and 2900), and dimethyl-*p*-toluidine had b. p. 44°/0·3 mm., n_D^{20} 1·5460, $\lambda_{max.}$ 2530 and 3030 Å (ε 16,000 and 2300).

Reduction of NN-*Dimethylaniline.*—(*a*) The reduction was carried out according to method A given by Birch,[4] the sodium ethoxide being filtered off instead of being washed out with water. Sodium (53 g.; 2·3 mol.) was added during 1 hr. to a stirred solution of dimethylaniline (55 c.c.; 0·43 mol.) and ethanol (142 c.c.; 2.45 mol.) in liquid ammonia (1 l.). After 2 hr. the blue colour disappeared, whereupon light petroleum (0·5 l.) was run in, and the ammonia allowed to boil off under nitrogen. The mixture was filtered, concentrated *in vacuo*, filtered again, and distilled *in vacuo* to give crude 2,3-dihydro-*NN*-dimethylaniline (34 g.; 65%), b. p. 66—70°/12 mm., n_D^{24} 1·531, $\lambda_{max.}$ 3040 Å (ε 7400). Treatment with 2,4-dinitrophenylhydrazinium chloride in methanol at 17° afforded the cyclohex-3-enone derivative, crystallising from ethanol in yellow plates, m. p. 132—133° (Birch [4] records m. p. 131—132°), and treatment with the boiling reagent gave the cyclohex-2-enone derivative, crystallising from ethanol in red needles, m. p. 164—166° (Birch [4] gives m. p. 165—166°).

(*b*) In a similar preparation, the product, in light petroleum, was filtered, washed briefly with dilute alkali, dried (Na_2SO_4), and distilled *in vacuo* to give a crude mixture, b. p. 55—100°/7 mm. (26 g.; 50%) which was fractionated. The forerun, b. p. up to 43·5°/3·5 mm. (1·2 g.), n_D^{20} 1·485, $\lambda_{max.}$ 3020 Å (ε 800), contained cyclohex-3-enone (ν 1720 cm.$^{-1}$), and the main fraction, b. p. 47·5—49°/3·5 mm. (8·3 g.), n_D^{20} 1·534, $\lambda_{max.}$ 3000 Å (ε 7000), consisted mainly of 2,3-dihydro-*NN*-dimethylaniline (ν 715, 1580, 1635, and 3035 cm.$^{-1}$).

This fraction was dissolved in water (25 c.c.) containing oxalic acid (4·3 g. of dihydrate), and next morning the solution was extracted with ether to recover crude cyclohex-3-enone (0·9 g.), n_D^{21} 1·463, $\lambda_{max.}$ 2250 and 2830 Å (ε 900 and 21). Adkins and Watkins [9] give $\lambda_{max.}$ 2250 (ε 10,200) for cyclohex-2-enone, so that $\not>$9% of this isomer was present in the hydrolysis product.

Reduction of NN-*Dimethyl*-p-*toluidine.*—(a) The procedure described by Wilds and Nelson [7] was adapted by using lithium (2·2 g.; 0·32 mol.), *NN*-dimethyl-*p*-toluidine (11 c.c.; 0·075 mol.), and ethanol (22 c.c.) in ether (30 c.c.) and liquid ammonia (160 c.c.). The product, b. p. 30—41°/0·5 mm., n_D^{20} 1·522, $\lambda_{max.}$ 2560 and 3020 Å (ε 3400 and 6900), contained unchanged dimethyltoluidine.

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[8] Elderfield, " Heterocyclic Compounds," Chapman and Hall Ltd., London, 1951, p. 230.

[9] Adkins and Watkins, *J. Amer. Chem. Soc.*, 1951, **73**, 2184.

(b) 2,3-*Dihydro*-NN-*dimethyl*-p-*toluidine*. Sodium (51·5 g.; 2·24 mol.) was added to a solution of *NN*-dimethyl-*p*-toluidine (55 c.c.; 0·38 mol.) and ethanol (150 c.c.) in liquid ammonia (1 l.) during ½ hr. The mixture was stirred overnight and diluted with light petroleum, and after the remaining ammonia had boiled away, sufficient ice was added to dissolve the alkali. The solvent layer was washed briefly, dried (Na_2SO_4), and distilled under nitrogen to give the crude amine, b. p. 43—50°/1 mm. (46 g.), $\lambda_{max.}$ 3010 Å (ε 8050). This was fractionated to obtain four fractions: (A) (8 g.), b. p. 42—51°/0·8 mm., n_D^{20} 1·500, $\lambda_{max.}$ 3010 Å (ε 3550); (B) (4·3 g.), b. p. 51—53°/0·8 mm., n_D^{20} 1·519, $\lambda_{max.}$ 3010 Å (ε 7500); (C) 17·4 g., b. p. 53—54°/0·8 mm., n_D^{20} 1·532, $\lambda_{max.}$ 3010 Å (ε 10,000); (D) 7·3 g., b. p. 54°/0·8 mm., n_D^{20} 1·534, $\lambda_{max.}$ 3010 Å (ε 10,500). Fraction (D) was essentially pure 2,3-*dihydro*-NN-*dimethyl*-p-*toluidine* (II) (Found: C, 78·6; H, 11·0. $C_9H_{15}N$ requires C, 78·8; H, 11·0%), ν 780, 1595, 1650, and 3030 cm.$^{-1}$.

Hydrolysis of this enamine (3·5 g.) with oxalic acid dihydrate (1·7 g.) in water (10 c.c.) was exothermic and gave, after distillation of the ether extract, 4-methylcyclohex-3-enone, b. p. 54—55°/10 mm., n_D^{21} 1·4715 (V; 2·1 g., 84%), $\lambda_{max.}$ 2260 and 2850 Å (ε 180 and 27). The 2,4-dinitrophenylhydrazone, prepared at 0°, crystallised from ethanol in orange needles, m. p. 131—134° (Found: C, 53·5; H, 4·85; N, 19·3. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·85; N, 19·3%), $\lambda_{max.}$ 3600 Å (ε 22,400 in ethanol). Birch[4] gives m. p. 120—121°, $\lambda_{max.}$ 3680 Å (ε 20,200 in chloroform). At the b. p. of the reagent, the derivative of 4-methylcyclohex-2-enone was produced instead, and this, after being filtered through alumina, crystallised from benzene–light petroleum in crimson needles, m. p. 172—175°, $\lambda_{max.}$ 2530 and 3750 Å (ε 16,000 and 28,000; in ethanol). Birch[4] gives m. p. 173—174°, $\lambda_{max.}$ 3830 (ε 22,200; in chloroform).

(c) *Effect of potassium amide on* 2,3-*dihydro*-NN-*dimethyl*-p-*toluidine* (II). Largely unchanged material (5·8 g.), b. p. 42—48°/0·7 mm., n_D^{20} 1·529, $\lambda_{max.}$ 3010 Å (ε 9600), was recovered after the enamine (II; 8·2 g.) had been treated with potassium amide (from the metal, 0·65 g.) in liquid ammonia (200 c.c.). Hydrolysis of the product with aqueous oxalic acid yielded impure 4-methylcyclohex-3-enone, b. p. 63—69°/14 mm., n_D^{20} 1·472, hydrogenation of which over 2·5% palladium–calcium carbonate in ethanol led to the uptake of hydrogen (0·90 molar equiv.), indicating the presence of 10% of 4-methylcyclohexanone in the original ketone.

(d) *The minor components of the product of the Birch reduction.* Two reductions were performed on twice the scale of experiment (b). In the first reduction, the product (93 g.), b. p. 32—54°/1 mm., n_D^{20} 1·518, $\lambda_{max.}$ 3020 Å (ε 7600), was fractionated and lower-boiling components, b. p. 30—43·5°/0·6 mm. (22·2 g.), collected, leaving a residue of 2,3-dihydro-amine (II) (61 g.; n_D^{20} 1·531). In the second reduction, the product (92 g.), b. p. 42—58°/1·2 mm., n_D^{20} 1·518, $\lambda_{max.}$ 3010 Å (ε 7800), was similarly fractionated to obtain a forerun (23·2 g.), b. p. 44—52·5°/1·5 mm., leaving a residue (II) (60 g.; n_D^{20} 1·530). These foreruns were combined and fractionated to obtain three fractions: (A) 1·9 g., b. p. 30—34°/1·5 mm., n_D^{20} 1·464, $\lambda_{max.}$ 3020 Å (ε 390); (B) 5·5 g., b. p. 34—38°/1·5 mm., n_D^{20} 1·471, $\lambda_{max.}$ 3000 Å (ε 740); (C) 7 g., b. p. 38—42°/1·5 mm., n_D^{20} 1·478, $\lambda_{max.}$ 3000 Å (ε 970). Fraction (B) afforded 4-methylcyclohexanone 2,4-dinitrophenylhydrazone, m. p. 133—134°, $\lambda_{max.}$ 2275 and 3610 Å (ε 17,000 and 24,000; in ethanol). Fraction (C) (6·9 g.) was hydrolysed by shaking its solution in light petroleum (110 c.c.) with oxalic acid dihydrate (3·5 g.) in water (30 c.c.) for 10 min., and the washed and dried petrol extract was distilled to give impure 4-methylcyclohexanone (4 g., 73%), b. p. 59—60°/14 mm., n_D^{19} 1·451, $\lambda_{max.}$ 2800 Å (ε 25). The absorption intensity at 2250 Å indicated $\not>$1% of 4-methylcyclohex-2-enone. Catalytic hydrogenation of this ketone involved the absorption of hydrogen (40 c.c. at 22°/761 mm.; 0·00167 mol.) equivalent to 4-methylcyclohex-3-enone (V) (0·184 g.; 19%).

It was concluded from these observations that the Birch reduction of dimethyl-*p*-toluidine yielded principally the 2,3-dihydro-amine (II) with smaller amounts of the 2,5-dihydro- and 3,4,5,6-tetrahydro-amines.

7,8-*Dihydro*-2,6-*dimethylchromone* (IV).—2,3-Dihydro-*NN*-dimethyl-*p*-toluidine (II; 8 g.; 0·058 mol.) in ether (100 c.c.) was mixed with redistilled diketen (8·6 c.c.; 0·117 mol.) at 0° under carbon dioxide. After 72 hr. at 0°, a white precipitate, m. p. 50—65° (4·9 g.), was removed but it could not be purified by crystallisation. The filtrate was concentrated *in vacuo* below 0°, whereupon an exothermal reaction occurred. The residual brown oil was taken up in a little ether and colourless needles of 7,8-*dihydro*-2,6-*dimethylchromone* (IV), m. p. 113—122° (2·4 g.; 24%), separated. Crystallisation from benzene–light petroleum gave the pure compound, m. p. 121—122·5° (Found: C, 74·7; H, 6·85. $C_{11}H_{22}O_2$ requires C, 75·0; H, 6·86%),

$\lambda_{max.}$ 2305 and 2785 Å (ε 14,500 and 9800; in ethanol), ν 805, 850, 920, 1630, 1645, 1670, and 3050 cm.$^{-1}$.

5,6,7,8-*Tetrahydro*-2,6-*dimethylchromone*.—The dihydrochromone (IV; 0·853 g.) was hydrogenated in ethanol over 2·5% palladium–calcium carbonate (0·5 g.) and hydrogen (113 c.c. at 20°/766 mm.; 0·0473 mol.) was absorbed, equivalent to 98% reduction to 5,6,7,8-*tetrahydro*-2,6-*dimethylchromone*, which was isolated, by filtration and removal of solvent *in vacuo*, as prisms, m. p. 60—83° (0·83 g.; 98%). Recrystallisations from benzene–light petroleum afforded pure material, m. p. 85—87° (Found: C, 74·4; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%), $\lambda_{max.}$ 2140 and 2535 Å (ε 8400 and 12,500 in ethanol), ν 850, 1615, 1635, and 1670 cm.$^{-1}$.

2,6-*Dimethylchromone*.—(*a*) 7,8-dihydro-2,6-dimethylchromone (IV; 0·5 g.) was dehydrogenated by refluxing it vigorously with *p*-cymene (3 c.c.) and 5% palladised charcoal (0·2 g.) for 2 hr. The suspension was filtered hot, the solvent removed from the filtrate *in vacuo*, and the residue crystallised from light petroleum to give crude 2,6-dimethylchromone, m. p. 77—97° (0·4 g.). Repeated crystallisation gave the pure compound, m. p. 100—101° (Found: C, 75·8; H, 5·8. Calc. for $C_{11}H_{10}O_2$: C, 75·8; H, 5·8%), $\lambda_{max.}$ 2260 and 3030 Å (ε 25,000 and 6400 in ethanol), ν 810, 845, 1635, and 1655 cm.$^{-1}$. Ruhemann [10] records m. p. 103—104°. There was no m. p. depression with the synthetic sample described below, and their infrared spectra were identical.

(*b*) Following the procedure [11] given for 2-phenoxycrotonic acid, sodium (0·3 g.; 0·013 mol.) was dissolved in *p*-cresol (20·5 g.) at 100°, and methyl tetrolate (5·3 g.; 0·054 mol) was added. When the exothermic reaction was over, ice was added, the product extracted with ether, and the recovered oil hydrolysed by potassium hydroxide (10 g.) in 75% aqueous methanol (80 c.c.) for 20 hr. The solution was acidified with hydrochloric acid in slight excess and speedily extracted with ether to give 2-*p*-tolyloxycrotonic acid, which crystallised from benzene–light petroleum in prisms, m. p. 152°, solidifying and remelting a t168° (3·7 g.; 36%) (Found: C, 68·9; H, 6·45. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%). Ruhemann [10] gives m. p. 145°, solidifying and remelting at 159—160°.

Following Gottesmann's method,[12] 2-*p*-tolyloxycrotonic acid (1 g.) was refluxed for 10 min. with acetyl chloride (10 c.c.) and concentrated sulphuric acid (5 drops). The solution was concentrated to about 3 c.c. and stored with concentrated sulphuric acid (5 c.c.) overnight; it was then poured into ice–water and extracted with ether to give 2,6-dimethylchromone, crystallising from light petroleum in needles, m. p. 99—102°. Recrystallisation yielded the pure material, m. p. 101—103° (50 mg.).

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[10] Ruhemann, *Ber.*, 1920, **53**, 285.
[11] Jones and Whiting, *J.*, 1949, 1430.
[12] Gottesmann, *Ber.*, 1933, **66**, 1168.