240. *Synthetic Analgesics and Related Compounds. Part IV.* Mannich Bases from Phenyl-substituted Acetones.*

By Walter Wilson and Zu-Yoong Kyi.

The series of Mannich bases (II; R′ = H), (VI), and (VII) have been obtained from 1 : 1-diphenylacetone, 1 : 3-diphenylacetone, and phenylacetone, respectively. The structure (II; R′ = H) was proved by degradation to the vinyl ketone (III) and to the methoxy-ketone (IV). The latter was not identical with the isomer (V) made by an unequivocal method. The bases (II; R′ = H) were unstable in neutral or alkaline solutions, and the vinyl ketone (III) appeared to be formed. Degradation of the bases (VII) afforded the αβ-unsaturated ketone (IX), which rapidly dimerised to the dihydropyran (X); the latter was also obtained as a by-product during the preparation of the bases (VII) from phenylacetone. The new bases are not analgesic, but several are potent local anæsthetics.

Few analogues of amidone, in which the side-chain length has been varied, are known; several δ- and ε-dialkylamino-ketones of this series had no analgesic activity (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500). It seemed possible that closely related bases (I) could be made from 1 : 1-diphenylacetone by the Mannich reaction; the products, however, were the isomers (II; R′ = H), as alkaline degradation of their quaternary salts gave the vinyl ketone (III). The structure of the latter was confirmed by the formation of a dibromide and by the intense light absorption at 210 mμ (ε > 23 000) (Fig. 2*c*); it was not identical with 4 : 4-diphenylbut-3-en-2-one (III*a*) (Klages and Fanto, *Ber.*, 1899, **32**, 1435), which could possibly arise from (I) by a carbonium-ion rearrangement (cf. Charlton, Dostrovsky, and Hughes, *Nature*, 1951, **167**, 986). The *cyclo*butanone structure (III*b*) was excluded as heating the ketone with aqueous sodium hydroxide gave a polymer and no carboxylic acid (cf. Bergmann and Blum-Bergmann, *J.*, 1938, 728). The methochloride of (II; R = Me, R′ = H) with methanolic sodium methoxide gave the methoxy-ketone (IV), which differed from the isomer (V) made by an unequivocal method (see below). These degradation experiments establish the structures (II; R′ = H) for the original bases, the Mannich reaction having taken place at position 3 of 1 : 1-diphenylacetone and not at position 1.† This result is not surprising, for although 1 : 1-diphenylacetone can be alkylated at position 1 (Tiffeneau and Levy, *Bull. Soc. chim.*, 1923, [4], **33**, 776; Part III), it condenses with benzaldehyde at position 3 (Staudinger and Rheiner, *Helv. Chim. Acta*, 1924, **7**, 15). Furthermore, 1-methyl-1 : 1-diphenylacetone readily forms Mannich bases (Zaugg, Freifelder, and Horrom, *J. Org. Chem.*, 1950, **15**, 1191), but diphenylmethyl phenyl ketone does not.

$CH_3{\cdot}CO{\cdot}CPh_2{\cdot}CH_2{\cdot}NR_2$ (I) $\quad$ $Ph_2CR'{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR_2$ (II)

$Ph_2CH{\cdot}CO{\cdot}CH{:}CH_2$ (III) $\quad$ $Ph_2C{:}CH{\cdot}CO{\cdot}CH_3$ (III*a*) $\quad$ $Ph_2C\text{—}CO{\cdot}CH_2\text{—}CH_2$ (III*b*)

$Ph_2CH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}OMe$ (IV) $\quad$ $CH_3{\cdot}CO{\cdot}CPh_2{\cdot}CH_2{\cdot}OMe$ (V)

The ultra-violet absorption (Figs. 1*a* and 2*a*) of (II; R′ = H, R = Et) in acid solution indicated a 1 : 1-diphenylacetone structure (Kumler, Strait, and Alpen, *J. Amer. Chem. Soc.*, 1950, **72**, 1463), but the spectra do not appear to allow the 1- and the 3-substituted isomers to be differentiated. Very dilute solutions of the hydrochloride of (II; R = Et, R′ = H) soon developed intense absorption bands; this change was rapid in the presence of alkali (Fig. 2*b*) and is believed to be caused by partial conversion of the compound into (III), whose extinction curve is also given (Fig. 2*c*).

Contrary to Avison and Morrison's experience (*J.*, 1950, 1475) with benzyl ketones, no

* Part III, *J.*, 1952, 6.

† *Added in Proof.*—Protiva and Jílek (*Coll. Czech. Chem. Comm.*, 1951, **16**, 151) draw the same conclusion about the structures of the Mannich bases.

difficulty was experienced in making the series of Mannich bases (VI) and (VII) from 1 : 3-diphenylacetone and phenylacetone, respectively. It is possible that the anomalies encountered by these authors were due to the amine components used, as it is well known that certain amines undergo the Mannich reaction with difficulty (*e.g.*, "Org. Reactions," 1942, **1**, 307). Avison and Morrison prepared a Mannich base, shown to be (VII; NR_2 = $NMe{\cdot}CH_2{\cdot}CH{:}CH_2$), from phenylacetone. The bases now obtained from phenylacetone were also assigned the structure (VII), because they were convertible into the pyrazoline obtained by Avison and Morrison from their base, and the iodoform tests were positive.

FIG. 1.

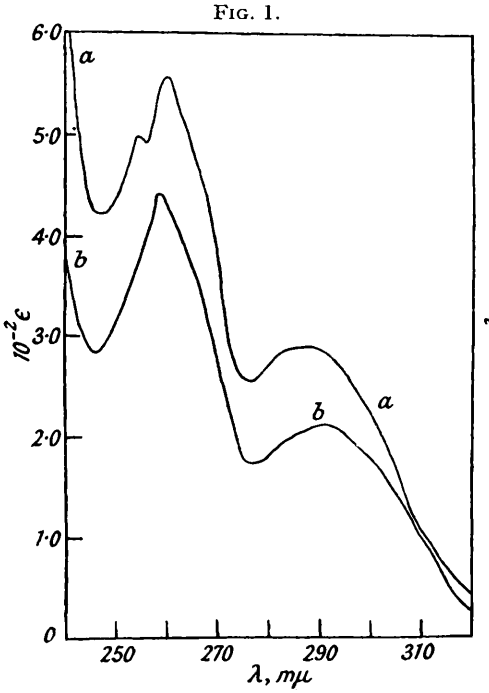


FIG. 2.

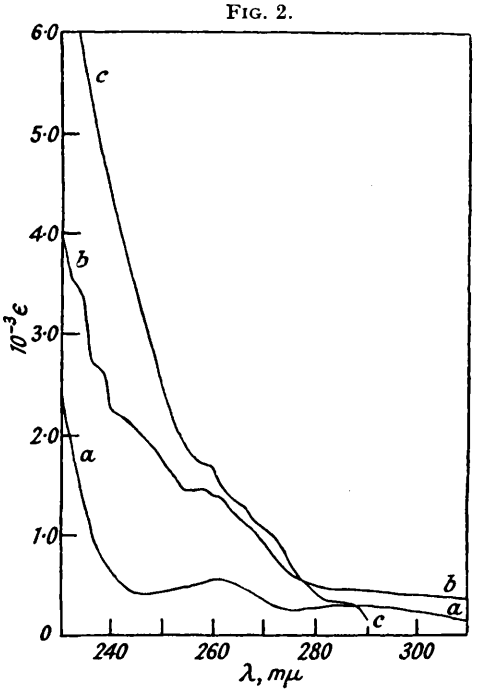


FIG. 1. a, 4-*Diethylamino*-1 : 1-*diphenylbutan*-2-*one hydrochloride in* N/100-*ethanolic hydrogen chloride*. $\lambda_{max.}$ (mμ) : 254 (ε = 498), 260 (ε = 558), 287 (ε = 280). $\lambda_{min.}$ (mμ) : 246 (ε = 422), 256 (ε = 491), 276 (ε = 257).

b, 4-*Methoxy*-3 : 3-*diphenylbutan*-2-*one in ethanol*. $\lambda_{max.}$ (mμ) : 258 (ε = 442), 290 (ε = 214). $\lambda_{min.}$ (mμ) : 246 (ε = 284), 276 (ε = 174).

FIG. 2. a, 4-*Diethylamino*-1 : 1-*diphenylbutan*-2-*one hydrochloride* (*details as for Fig.* 1, *curve* a).

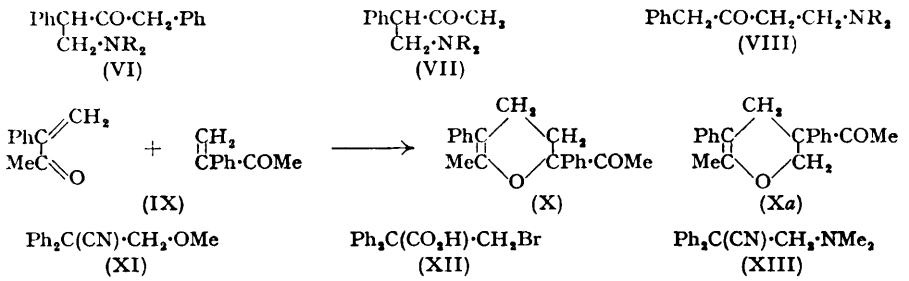
b, 4-*Diethylamino*-1 : 1-*diphenylbutan*-2-*one hydrochloride in ethanol* (75·2 *mg./l.*). *Solution set aside for* 24 *hours, then* N/10-*aqueous potassium hydroxide* (8 *c.c./l.*) *added, and spectrum measured immediately. Inflexion at* 258 mμ (ε = 1480).

c, 1 : 1-*Diphenylbut*-3-*en*-2-*one in ethanol*. $\lambda_{max.}$ (mμ) : 210 (ε > 23 000).

Aqueous alkali converted the methiodide of (VII; R = Me) into the αβ-unsaturated ketone (IX), which rapidly dimerised to the crystalline dihydropyran (X; or less probably X*a*). The same dihydropyran was formed (5—6%) as a by-product during the preparation of Mannich bases from phenylacetone. The dihydropyran structure was confirmed by the molecular weight, the formation of a mono-oxime, the positive iodoform reaction, and the presence of an inert (non-hydroxylic) oxygen atom. Analogous dimers have been obtained from αβ-unsaturated carbonyl compounds by Alder, Offermanns, and Rüden (*Ber.*, 1941, **74**, 926). It is probable that the compound $C_{18}H_{16}O_2$, m. p. 172°, obtained by alkaline degradation of 3-dimethylamino-1-phenylpropan-1-one methiodide (Jacob and Madinaveitia, *J.*, 1937, 1929) is similarly a dihydropyran formed by dimerisation of phenyl vinyl ketone.

Several unsuccessful attempts to synthesise β-dialkylamino-ketones by alternative

methods were made. Thus, diphenylmethyl cyanide and methoxymethyl bromide readily afforded the cyanide (XI), which yielded the methoxy-ketone (V) with methylmagnesium iodide. The methoxy-ketone could not be demethylated in boiling hydrobromic acid, but the required bromo-ketone may be obtainable from the corresponding acid (XII)



recently described (Zaugg, *J. Amer. Chem. Soc.*, 1950, **72**, 2998). Böckmuhl and Ehrhart (*Annalen*, 1948, **561**, 52) failed to ketonise the basic cyanide (XIII) in an attempt to make (I; R = Me). We failed to obtain ketonic products from 2-diethylaminoethyl cyanide and benzylmagnesium chloride (cf. Clarke and Mosher, *J. Amer. Chem. Soc.*, 1950, **72**, 1026).

The Mannich bases described were examined for biological activity in Dr. P. B. Marshall's laboratory (see acknowledgments). The compounds are not analgesic, but several are potent local anæsthetics. Thus (II; R′ = H, R = Me) and (VI; NR_2 = piperidino) are from 4 to 5 times as active as procaine on comparison by Bülbring and Wajda's method (*J. Pharmacol. Exper. Therap.*, 1945, **85**, 78), and their therapeutic indices are comparable with the value for cinchocaine B.P. These Mannich bases may be too unstable in solution for clinical use.

Experimental

4-Dimethylamino-1 : 1-diphenylbutan-2-one (II; R = Me, R′ = H).—A mixture of 1 : 1-diphenylacetone (105 g.), dimethylammonium chloride (65 g.), paraformaldehyde (24 g.), concentrated hydrochloric acid (3 c.c.), and ethanol (300 c.c.) was boiled under reflux for 16 hours. Excess of water was added and unreacted ketone (22 g., 21%) removed by ether extraction. The aqueous solution was made alkaline and the liberated base isolated by ether extraction. Treatment of the base with ethanolic hydrogen chloride gave the *hydrochloride* (76 g., 50% yield); this had m. p. 157—158° after recrystallisation from ethanol (Found: C, 70·9; H, 7·1; N, 4·8; Cl, 11·6. $C_{18}H_{21}ON,HCl$ requires C, 71·2; H, 7·25; N, 4·6; Cl, 11·7%). The iodoform test was negative as with 1 : 1-diphenylacetone. The *picrate* formed needles, m. p. 120—121°, from ethanol–ethyl acetate (Found: C, 57·8; H, 4·6. $C_{24}H_{24}O_8N_4$ requires C, 58·1; H, 4·8%), and the *methiodide* crystallised from ethanol as flakes, m. p. 145° (decomp.) (Found: C, 55·7; H, 6·1; I, 31·5. $C_{18}H_{21}ON,CH_3I$ requires C, 55·7; H, 5·9; I, 31·1%). The hydrochloride (45 g.) was converted into the base, which was dissolved in ethanol (250 c.c.) and saturated with gaseous methyl chloride; the somewhat impure *methochloride* (40 g., 85%) separated as needles, m. p. 145°, after being recrystallised from aqueous methanol (Found: C, 74·1; H, 7·0. $C_{19}H_{24}ONCl$ requires C, 71·8; H, 7·6%).

Slight modifications of the above procedure were used for making the following Mannich bases from the appropriate ketones and secondary amine hydrochlorides; in some cases (*A*) the hydrochlorides were isolated as above, in others (*B*) they crystallised out from the reaction mixture; the reaction times and the percentage yields are stated in each example.

4-Diethylamino-1 : 1-diphenylbutan-2-one hydrochloride (16 hours; *A*; 39%), m. p. 114—115° (Found: C, 72·3; H, 7·7; Cl, 10·55. $C_{20}H_{25}ON,HCl$ requires C, 72·4; H, 7·8; Cl, 10·7%); *picrate*, glistening flakes, m. p. 122—123° (from ethanol–ethyl acetate) (Found: C, 60·1; H, 5·3. $C_{20}H_{25}ON,C_6H_3O_7N_3$ requires C, 59·6; H, 5·3%).

1 : 1-Diphenyl-4-piperidinobutan-2-one hydrochloride (4 hours; *A*; 17%, with 72% of unreacted 1 : 1-diphenylacetone), m. p. 196—197° (from ethanol) (Found: C, 73·3; H, 7·2; N, 3·9; Cl, 10·1. $C_{21}H_{25}ON,HCl$ requires C, 73·35; H, 7·6; N, 4·1; Cl, 10·3%), was only slightly soluble in water. The *picrate* (from ethanol–ethyl acetate) had m. p. 150—151° (Found: C, 60·6; H, 5·4. $C_{21}H_{25}ON,C_6H_3O_7N_3$ requires C, 60·4; H, 5·2%).

4-*Morpholino*-1 : 1-*diphenylbutan*-2-*one hydrochloride* (16 hours; *A*; 49%, with 46% of unreacted ketone), m. p. 183—184° (Found : Cl, 10·3. $C_{20}H_{23}O_2N$,HCl requires Cl, 10·3%), was very sparingly soluble in water and ethanol. The *picrate* formed needles, m. p. 139—140°, from ethanol–ethyl acetate (Found : C, 57·9; H, 5·0. $C_{20}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 58·0; H, 4·8%); the *methiodide* had m. p. 137—138° (from ethanol) (Found : C, 55·3; H, 5·4; I, 28·4. $C_{20}H_{23}O_2N,CH_3I$ requires C, 55·9; H, 5·8; I, 28·2%).

4-*Dimethylamino*-1 : 3-*diphenylbutan*-2-*one hydrochloride* (4 hours; *B*; 57%) formed needles, m. p. 163—164°, from ethanol (Found : C, 71·1; H, 7·3; N, 4·8; Cl, 11·6. $C_{18}H_{21}ON$,HCl requires C, 71·2; H, 7·25; N, 4·6; Cl, 11·7%). Doubling the proportions of paraformaldehyde and dimethylammonium chloride increased the yield to 77%. The *picrate*, m. p. 105—106°, formed needles from ethanol–ethyl acetate (Found : C, 58·1; H, 4·8. $C_{18}H_{21}ON,C_6H_3O_7N_3$ requires C, 58·1; H, 4·8%), and the *methiodide* had m. p. 129—130° (from acetone) (Found : I, 31·4. $C_{18}H_{21}ON,CH_3I$ requires I, 31·1%); the latter compound slowly decomposed.

4-*Diethylamino*-1 : 3-*diphenylbutan*-2-*one hydrochloride* (4 hours; *A*; 13%) had m. p. 115—116° (from acetone) (Found : C, 72·1; H, 7·5; Cl, 10·5. $C_{20}H_{25}ON$,HCl requires C, 72·4; H, 7·8; Cl, 10·7%), and the *picrate*, m. p. 97—98° (needles from ethanol–ethyl acetate) (Found : C, 59·7; H, 5·3. $C_{20}H_{25}ON,C_6H_3O_7N_3$ requires C, 59·55; H, 5·3%).

1 : 3-*Diphenyl*-4-*piperidinobutan*-2-*one hydrochloride* (4 hours; *B*; 30%) formed sparingly soluble needles, m. p. 162—163°, from ethanol (Found : C, 73·1; H, 7·3; N, 4·3; Cl, 10·3. $C_{21}H_{25}ON$,HCl requires C, 73·35; H, 7·6; N, 4·1; Cl, 10·3%). The *base*, recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), had m. p. 71—71·5° (Found : C, 82·5; H, 7·6. $C_{21}H_{25}ON$ requires C, 82·1; H, 8·1%), and the *picrate* formed prisms, m. p. 116—117° (from 80% ethanol) (Found : C, 60·6; H, 5·0. $C_{21}H_{25}ON,C_6H_3O_7N_3$ requires C, 60·4; H, 5·2%).

4-*Morpholino*-1 : 3-*diphenylbutan*-2-*one hydrochloride* (4 hours; *B*; 59%) crystallised from 80% methanol as cubes, m. p. 170—171° (Found : Cl, 10·2. $C_{20}H_{23}O_2N$,HCl requires Cl, 10·3%). The *base* formed needles, m. p. 75—75·5°, from ethyl acetate–light petroleum (b. p. 60—80°) (Found : C, 77·4; H, 7·4. $C_{20}H_{23}O_2N$ requires C, 77·65; H, 7·45%), and the *picrate*, flakes, m. p. 155·5—156°, from 80% methanol (Found : C, 57·8; H, 4·6. $C_{20}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 58·0; H, 4·8%).

4-*Dimethylamino*-3-*phenylbutan*-2-*one hydrochloride* (4 hours; *B*; 61%) formed colourless cubes, m. p. 155—156°, from *iso*propanol (Found : C, 63·3; H, 7·9; N, 6·0; Cl, 15·5. $C_{12}H_{17}ON$,HCl requires C, 63·3; H, 7·9; N, 6·15; Cl, 15·6%); the iodoform test was positive. Treatment with sodium hydroxide afforded the *base*, b. p. 91—93°/0·05 mm. (Found : C, 75·8; H, 8·7; N, 7·0. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%), which slowly evolved dimethylamine. The *picrate* formed needles, m. p. 98—99°, from ethanol–ethyl acetate (Found : C, 51·6; H, 4·9. $C_{12}H_{17}ON,C_6H_3O_7N_3$ requires C, 51·4; H, 4·8%), and the *methiodide* had m. p. 190—191° from water (Found : C, 46·5; H, 5·8; N, 4·3; I, 38·0. $C_{12}H_{17}ON,CH_3I$ requires C, 46·8; H, 6·0; N, 4·2; I, 38·15%).

4-*Diethylamino*-3-*phenylbutan*-2-*one hydrochloride* (4 hours; *A*; 22%) had m. p. 123·5—124·5° (from acetone–ethanol) (Found : C, 65·8; H, 8·4; Cl, 13·9. $C_{14}H_{21}ON$,HCl requires C, 65·75; H, 8·6; Cl, 13·9%); the *picrate* had m. p. 78·5—79·5° (prisms from ethanol) (Found : C, 54·0; H, 5·3. $C_{14}H_{21}ON,C_6H_3O_7N_3$ requires C, 53·6; H, 5·35%) and the *methiodide* m. p. 113—114° (from *iso*propanol) (Found : C, 49·6; H, 6·7. $C_{14}H_{21}ON,CH_3I$ requires C, 49·9; H, 6·65%).

3-*Phenyl*-4-*piperidinobutan*-2-*one hydrochloride* (4 hours; *B*; 52%) formed colourless cubes, m. p. 157—158°, from acetone–ethanol (Found : C, 67·2; H, 8·0; N, 5·5; Cl, 13·2. $C_{15}H_{21}ON$,HCl requires C, 67·3; H, 8·2; N, 5·2; Cl, 13·3%). The *base*, m. p. 40·5—41°, was recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) (Found : C, 77·4; H, 8·7. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1%); the *picrate* had m. p. 107—108° (glistening flakes from ethanol) (Found : C, 54·6; H, 4·9. $C_{15}H_{21}ON,C_6H_3O_7N_3$ requires C, 54·8; H, 5·2%) and the *methiodide* m. p. 152—153° (from acetone–ethanol) (Found : C, 51·5; H, 6·4; I, 34·1. $C_{15}H_{21}ON,CH_3I$ requires C, 51·5; H, 6·4; I, 34·05%).

4-*Morpholino*-3-*phenylbutan*-2-*one hydrochloride* (4 hours; *B*; 70%) crystallised in cubes, m. p. 175—176°, from 80% methanol (Found : Cl, 13·0. $C_{14}H_{19}O_2N$,HCl requires Cl, 13·2%). The *base*, crystallised from ethyl acetate–light petroleum (b. p. 60—80°), had m. p. 51—52° (Found : C, 72·1; H, 8·1. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2%), the *picrate* m. p. 119—120° (prisms from ethanol) (Found : C, 51·95; H, 4·8. $C_{14}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 51·9; H, 4·8%), and the *perchlorate* m. p. 151—152° (needles from ethanol) (Found : C, 50·8; H, 5·8. $C_{14}H_{19}O_2N,HClO_4$ requires C, 50·4; H, 6·0%).

Degradation of 4-*Dimethylamino*-1 : 1-*diphenylbutan*-2-*one Methochloride*.—(a) *With sodium*

hydroxide. The methochloride (20 g.) was stirred with sodium hydroxide (10 g.) in water (300 c.c.) for 1 hour at 25°. Extraction with benzene and distillation afforded 1 : 1-*diphenylbut-3-en-2-one* (III) (6 g., 43% yield), b. p. 103—105°/0·01 mm., which gave crystals, m. p. 53—54°, from light petroleum (b. p. 60—80°) containing a little ethyl acetate (Found : C, 86·9; H, 6·4. $C_{16}H_{14}O$ requires C, 86·5; H, 6·3%). Hot concentrated sodium hydroxide polymerised this compound to a brittle glass. The ketone (0·5 g.) with a slight excess of bromine in chloroform at 30—35° afforded 3 : 4-*dibromo*-1 : 1-*diphenylbutan*-2-*one* (0·79 g., 92%), which formed needles, m. p. 79—80°, from light petroleum (b. p. 60—80°) (Found : C, 50·3; H, 3·9; Br, 41·9. $C_{16}H_{14}OBr_2$ requires C, 50·25; H, 3·7; Br, 41·9%).

(b) *With sodium methoxide.* The methochloride (5 g.) was dissolved in a mixture of methanol (100 c.c.) and benzene (30 c.c.), and a cold solution of sodium methoxide [from sodium (0·7 g.) and methanol (40 c.c.)] was added. After 90 minutes the mixture was poured into 3N-hydrochloric acid (200 c.c.), and the acid mixture extracted with benzene. Distillation of the extract afforded 4-*methoxy*-1 : 1-*diphenylbutan*-2-*one* (IV) (1·9 g., 47%), b. p. 120—122°/0·05 mm.; n_D^{22} 1·5611 (Found : C, 80·3; H, 7·1. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The *oxime* had m. p. 97—98° (Found : C, 76·5; H, 7·15. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%); a mixture with 4 : 4-diphenylbut-3-en-2-one oxime had a much lower melting point.

4 : 4-*Diphenylbut*-3-*en*-2-*one* (III*a*).—(Cf. Klages and Fanto, *Ber.*, 1899, **32**, 1435.) Redistilled diphenyldichloromethane (24 g.) was boiled for 6 hours with a suspension of dry cupric acetoacetate (32 g.) in absolute ethanol (50 c.c.). The mixture was diluted with ether and filtered, and the filtrate washed with dilute aqueous sodium hydroxide. Distillation afforded crude ethyl α-acetyl-ββ-diphenylacrylate (14·4 g.), b. p. 157—167°/0·02 mm., which solidified. The crude ester was boiled for 6 hours with potassium hydroxide (7 g.) in aqueous ethanol (35 c.c.). The alcohol was distilled off and neutral substances removed by ether extraction. Addition of hydrochloric acid precipitated α-acetyl-ββ-diphenylacrylic acid as an oil, which was isolated by extraction with benzene. The crude acid (10·5 g.) was heated at 15 mm. pressure; violent effervescence occurred, then a mobile oil (6·0 g.) distilled at 195—205°/15 mm. Redistillation gave 4 : 4-diphenylbut-3-en-2-one, b. p. 140°/0·015 mm.; n_D^{25} 1·6165, which gave an oxime, m. p. 92·5—94°, and a 2 : 4-*dinitrophenylhydrazone*, which formed bright red prisms, m. p. 153—154°, from ethanol (Found : N, 14·3. $C_{22}H_{18}O_4N_4$ requires N, 14·0%).

Degradation of 4-*Morpholino*-1 : 1-*diphenylbutan*-2-*one Methiodide.*—The methiodide (10 g.) was heated for 1 hour at 40—50° with 10% aqueous sodium hydroxide (100 c.c.). The oil was extracted with ether, and the ether layer shaken with excess of dilute hydrochloric acid. The crystals (4·4 g., 58%) which separated were 4-morpholino-1 : 1-diphenylbutan-2-one hydrochloride. The ethereal filtrate was washed with aqueous sodium hydrogen carbonate, dried, and distilled, affording 1 : 1-diphenylbut-3-en-2-one (0·9 g., 18%), b. p. 110—118°/0·04 mm., m. p. 53—54° after recrystallisation from light petroleum (b. p. 60—80°). The methiodide did not appear to react with 3% sodium hydroxide solution at 20°.

2-*Acetyl*-2 : 3-*dihydro*-6-*methyl*-2 : 5-*diphenylpyran* (X).—(a) *From the preparation of* 4-*dimethylamino*-3-*phenylbutan*-2-*one hydrochloride.* The liquors from which the hydrochloride had crystallised were diluted with excess of water and extracted with ether. The fraction of b. p. 130—140°/0·5 mm. was crystallised from aqueous methanol, and gave the *dihydropyran* (1·7 g., 6% yield) as white needles, m. p. 78—79° [Found : C, 82·7; H, 6·85%; *M* (Rast), 252. $C_{20}H_{20}O_2$ requires C, 82·2; H, 6·85%; *M*, 292]; ultra-violet extinction maximum at 247 mμ ($E_{1\,cm.}^{1\%}$ 247) in ethanol solution. The iodoform test (Fuson and Tullock's modification, *J. Amer. Chem. Soc.*, 1934, **56**, 1638) was strongly positive, and a solution of bromine in chloroform was decolorised rapidly in the cold with evolution of hydrogen bromide. The compound did not react with acetic anhydride in pyridine, and the *oxime*, prepared in 70% ethanol, formed prisms, m. p. 153° (Found : C, 78·5; H, 6·9; N, 4·8. $C_{20}H_{21}O_2N$ requires C, 78·2; H, 6·85; N, 4·6%).

(b) *By degradation of* 4-*dimethylamino*-3-*phenylbutan*-2-*one methiodide.* The methiodide (28 g.) was stirred with 3% aqueous sodium hydroxide (300 c.c.) at 20°. The oil which separated was extracted with benzene and distilled, giving 3-phenylbut-3-en-2-one (8·5 g., 69%), b. p. 54—55°/0·8 mm. This dimerised, before it could be analysed, to the solid dihydropyran (X), b. p. 133—136°/0·8 mm., m. p. 76—77° after recrystallisation from light petroleum (b. p. 60—80°) [Found : C, 82·0; H, 6·8. Calc. for $(C_{10}H_{10}O)_n$: C, 82·2; H, 6·85%]. The oxime had m. p. 154·5—155·5°, not depressed on admixture of the sample with the oxime obtained in (*a*).

3-*Methyl*-1 : 4-*diphenylpyrazoline.*—4-Dimethylamino-3-phenylbutan-2-one hydrochloride (3 g.), sodium acetate (3 g.), and phenylhydrazine (3 g.) were dissolved in a mixture of ethanol

(10 c.c.) and glacial acetic acid (10 c.c.), and the sodium chloride filtered off. The solution was boiled for 6 hours; the resulting pyrazoline formed pale yellow plates, m. p. 159—160°, from methanol (Avison and Morrison, *J.*, 1950, 1474, give m. p. 159—160°). The same pyrazoline was obtained from the other Mannich bases derived from phenylacetone.

2-*Methoxy*-1 : 1-*diphenylethyl Cyanide* (XI).—Diphenylmethyl cyanide (97 g.) was stirred at 30—35° with powdered sodamide (31 g.) in dry benzene (300 c.c.). Methoxymethyl bromide (87·5 g.) (Vavon, Bolle, and Calin, *Bull. Soc. chim.*, 1939, [5], **6**, 1032) in dry benzene (70 c.c.) was added slowly with cooling to 45—50°. The mixture was refluxed for 2 hours, then washed with water, and distilled. The fraction of b. p. 148—152°/0·1 mm. (73 g.) was recrystallised from *iso*propanol, yielding 2-*methoxy*-1 : 1-*diphenylethyl cyanide* (48 g., 41%), m. p. 56—57° (Found: C, 81·0; H, 6·5. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3%).

4-*Methoxy*-3 : 3-*diphenylbutan*-2-*one* (V).—The cyanide (XI) (35·6 g.) in toluene (80 c.c.) was mixed with a Grignard solution from magnesium (3·8 g.), methyl iodide (25 g.), and ether (60 c.c.). The ether was distilled off and the residual solution refluxed for 3 hours. Water (80 c.c.) and concentrated hydrochloric acid (50 c.c.) were added and the toluene layer separated and distilled. The fraction of b. p. 131—135°/0·1 mm. solidified and was recrystallised from methanol, affording the *methoxy-ketone* (14 g., 73%) as needles, m. p. 92·5—93·5° (Found: C, 80·4; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The compound did not appear to be demethylated by boiling 48% hydrobromic acid. The *oxime* was obtained by heating the ketone for 3 hours with hydroxylamine hydrochloride and sodium acetate in ethanol, and had m. p. 167—168° (Found: C, 76·1; H, 7·2. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%).

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