2. *Synthetic Analgesics and Related Compounds. Part III.* The Aminoalkylation of Phenyl-substituted Acetones.*

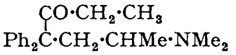
By Walter Wilson.

Several γ-dialkylamino-ketones, which had appreciable local anæsthetic activity, have been obtained from phenylacetone or 1 : 3-diphenylacetone by reaction with 2-dialkylaminoethyl chlorides and sodamide in benzene. Enol ethers were not detected in the products. A by-product from 1 : 3-diphenylacetone was the symmetrical bis-2-dimethylaminoethyl derivative (III). The alternative unsymmetrical structure (IV; $R = CO\cdot CH_2Ph$) was excluded by comparison with the authentic compound of the latter structure, made from 3-cyano-1 : 5-bisdimethylamino-3-phenylpentane (IV; R = CN) and benzylmagnesium chloride. The known analgesic, 5-dimethylamino-3 : 3-diphenylpentan-2-one (VI), was obtained in low yield from 1 : 1-diphenylacetone and 2-dimethylaminoethyl chloride.

A possible convenient source of γ-dialkylamino-ketones related to amidone (I) is the condensation between suitable α-phenyl-substituted ketones and 2-dialkylaminoalkyl halides. *C*-Alkylated products (II; R = Me or CH_2Ph) of the required structures have now been obtained from phenylacetone and from 1 : 3-diphenylacetone by treating it with 2-dimethylamino- and 2-diethylamino-ethyl chloride and sodamide in benzene. One of these products (II; R = Me, R′ = Et) has been described previously (Brown, Cook, and Heilbron, *J.*, 1949, S 106).

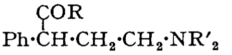
The bases were unchanged on prolonged boiling with concentrated hydrochloric acid, and they afforded highly crystalline homogeneous hydrogen oxalates. The bases are believed to be substantially free from enol ethers, which, if formed, had been hydrolysed during the subsequent operations. Basic ketones and enol ethers are both obtained in the related reaction of deoxybenzoin with 2-dialkylaminoethyl chlorides (Sperber, Fricano, and Papa, *J. Amer. Chem. Soc.*, 1950, **72**, 3068; Matti and Reynaud, *Bull. Soc. chim.*, 1951, **18**, 31). A secondary product from 1 : 3-diphenylacetone and 2-dimethylaminoethyl chloride was the symmetrical bis-2-dimethylaminoethyl derivative (III) : an enol ether structure was excluded by the stability of the compound to boiling concentrated hydrochloric acid, and the compound was not identical with the unsymmetrical alternative isomer (IV; $R = CO\cdot CH_2Ph$) made by an unequivocal method from the cyanide (IV; R = CN) and benzylmagnesium chloride. The cyanides (V; R′ = Me or Et) are ketonised by phenylmagnesium bromide (Sperber, Fricano, and Papa, Matti; and Reynaud, *locc. cit.*), but not by methylmagnesium iodide (Brown, Cook, and Heilbron, *loc. cit.*). The latter reaction would provide an alternative route to some of the ketones prepared here, but its failure has been confirmed.

1 : 1-Diphenylacetone reacted only slowly with 2-dimethylaminoethyl chloride, and 73% of the ketone was recovered. The basic condensation product was a mixture, from which 5-dimethylamino-3 : 3-diphenylpentan-2-one (VI) was isolated as the hydrochloride in only 3% overall yield. Tiffeneau and Levy (*Bull. Soc. chim.*, 1923, **33**, 776) also found that simple alkylations of 1 : 1-diphenylacetone occurred at position 1. Some 1 : 1-diphenylbutan-2-one was made by a new method from diphenylacetyl chloride and diethylcadmium, but it was decided not to treat this with 2-chloro-1-dimethylaminopropane



$\mathrm{Ph_2\overset{CO\cdot CH_2\cdot CH_3}{C}\cdot CH_2\cdot CHMe\cdot NMe_2}$

(I)



$\mathrm{Ph\cdot\overset{COR}{C}H\cdot CH_2\cdot CH_2\cdot NR'_2}$

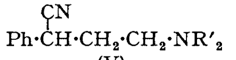
(II)

$\mathrm{CO(CHPh\cdot CH_2\cdot CH_2\cdot NMe_2)_2}$

(III)

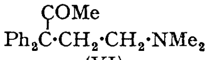
$\mathrm{Ph\cdot CR(CH_2\cdot CH_2\cdot NMe_2)_2}$

(IV)



$\mathrm{Ph\cdot\overset{CN}{C}H\cdot CH_2\cdot CH_2\cdot NR'_2}$

(V)



$\mathrm{Ph_2\overset{COMe}{C}\cdot CH_2\cdot CH_2\cdot NMe_2}$

(VI)

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* Part II, *J.*, 1951, 1706.

because it had become clear that only a minute yield of amidone could be expected, and because Walton, Ofner, and Thorpe (*J.*, 1949, 649) reported the failure of preliminary experiments to make amidone by this method.

Biological examination of the new basic ketones has so far revealed only local anæsthetic properties. The compound (II; R = CH_2Ph, R′ = Me) possessed about 0·4 times the activity of cinchocaine ("Nupercaine") on comparison by Bülbring and Wajda's method (*J. Pharmacol. Exper. Therap.*, 1945, **85**, 78).

EXPERIMENTAL

5-Dimethylamino-3-phenylpentan-2-one (II; R = R′ = Me).—Phenylacetone (26·8 g.), powdered sodamide (8·6 g.), and pure benzene (125 c.c.) were stirred at 25—30° for 15 minutes, then dry 2-dimethylaminoethyl chloride (21·5 g.) in benzene (25 c.c.) was added. On heating to 55°, a vigorous reaction commenced and was completed by stirring at 75—80° for 2 hours. The mixture was washed with water and extracted with 4N-hydrochloric acid. Phenylacetone (6·6 g., 25%) was recovered from the benzene phase, and an oily base (27·9 g.) from the acid extracts. Distillation afforded the *dimethylamino*-compound (23·2 g., 57%), b. p. 96°/1·4 mm., n_D^{20} 1·5040 (Found: C, 76·9; H, 9·2. $C_{13}H_{19}ON$ requires C, 76·1; H, 9·3%). The iodoform test was positive. The hydrochloride and picrate were not obtained crystalline. The base (2·05 g.), ethanol (5 c.c.), and oxalic acid dihydrate (1·3 g.; as a concentrated aqueous solution) afforded the *hydrogen oxalate* (1·25 g.), which formed white needles (from ethanol–acetone), m. p. 122·5° (Found: C, 61·35; H, 6·7. $C_{15}H_{21}O_5N$ requires C, 61·05; H, 7·1%). The base was unchanged after 6 hours in boiling concentrated hydrochloric acid, and the yield of hydrogen oxalate was not affected by this treatment. The base (4·1 g.), hydroxylamine hydrochloride (1·4 g.), acetic acid (0·3 c.c.), and ethanol (25 c.c.) were boiled for 6 hours. Evaporation and addition of ether afforded a solid (5·1 g.; m. p. 169—172°) which was recrystallised from *iso*propanol–ethyl acetate; the *oxime hydrochloride* had m. p. 173° (Found: C, 60·3; H, 8·35. $C_{13}H_{21}ON_2Cl$ requires C, 60·8; H, 8·2%).

5-Diethylamino-3-phenylpentan-2-one (II; R = Me, R′ = Et).—A similar reaction using phenylacetone and 2-diethylaminoethyl chloride afforded the diethylamino-compound, b. p. 134°/3 mm., n_D^{20} 1·4992, in 54% yield (Brown, Cook, and Heilbron, *loc. cit.*, give yield 43%, b. p. 102—105°/0·1 mm., n_D^{24} 1·4958). The iodoform test was positive, and the *hydrogen oxalate* was obtained in 77% yield in aqueous ethanol–ether and formed prisms, m. p. 125° (Found: N, 4·4. $C_{17}H_{25}O_5N$ requires N, 4·35%).

Reaction of 1 : 3-*Diphenylacetone with* 2-*Dimethylaminoethyl Chloride.*—Redistilled 1 : 3-diphenylacetone (26·3 g.), powdered sodamide (5·5 g.), and dry benzene (60 c.c.) were stirred for 30 minutes with cooling to below 30°. 2-Dimethylaminoethyl chloride (anhydrous) (13·4 g.) in benzene (15 c.c.) was added and the mixture warmed to 65—70°. When the vigorous reaction subsided, the mixture was stirred under reflux for 2¼ hours. Extraction with dilute hydrochloric acid afforded a neutral and a basic fraction. The neutral fraction (10·5 g.) was mainly 1 : 3-diphenylacetone, but crystals of impure stilbene (an artefact?) (0·5 g.), m. p. 115·5—117·5°, slowly separated (Found: C, 93·6; H, 7·0. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%); a mixture with authentic stilbene (m. p. 123°) had m. p. 117—122°. The solution of the basic fraction in dilute hydrochloric acid was evaporated to dryness and the solid extracted with hot absolute ethanol. Recrystallisation of the sparingly soluble portion from aqueous ethanol–acetone afforded 1 : 7-*bisdimethylamino*-3 : 5-*diphenylheptan*-4-*one dihydrochloride* (cf. III) (2·2 g.) as small prisms, m. p. 270° (decomp.) (Found: C, 65·0; H, 8·1. $C_{23}H_{32}ON_2,2HCl$ requires C, 64·95; H, 8·0%). The corresponding *dipicrate* formed bright yellow prisms, m. p. 196—197°, from aqueous acetone–ether (Found: N, 13·8. $C_{35}H_{38}O_{15}N_8$ requires N, 13·85%). The more soluble portion of the crude hydrochloride yielded 5-*dimethylamino*-1 : 3-*diphenylpentan*-2-*one hydrochloride* (10·6 g.), m. p. 149·5—151°, on crystallisation from *iso*propanol–ether (Found: C, 71·95; H, 7·7. $C_{19}H_{23}ON,HCl$ requires C, 71·8; H, 7·55%).

5-*Diethylamino*-1 : 3-*diphenylpentan*-2-*one* (II; R = CH_2Ph, R′ = Et).—A similar reaction between 1 : 3-diphenylacetone (17·4 g.), sodamide (3·5 g.), and 2-diethylaminoethyl chloride (11·2 g.) in benzene (55 c.c.) afforded a neutral fraction (11·2 g.) which was mainly 1 : 3-diphenylacetone, and a basic fraction. The latter was refluxed for 4 hours with concentrated hydrochloric acid, then isolated and distilled, yieding the 5-*diethylamino*-compound (9·0 g.), b. p. 152—154°/0·04 mm., n_D^{25} 1·5382 (Found: C, 81·55; H, 9·05. $C_{21}H_{27}ON$ requires C, 81·55; H, 8·75%). The hydrochloride was not obtained crystalline.

3-*Cyano*-1 : 5-*bisdimethylamino*-3-*phenylpentane* (IV; R = CN).—1-Cyano-3-dimethylamino-1-phenylpropane (9·4 g.) was stirred at 25—35° for 10 minutes with powdered sodamide (2·5 g.) in benzene (25 c.c.). 2-Dimethylaminoethyl chloride (anhydrous) (5·4 g.) in benzene (12 c.c.) was added and the reaction completed by boiling for 2 hours. The resulting *cyano*-base (9·4 g., 72·5%) had b. p. 116—120°/0·02 mm., n_D^{22} 1·5088 (Found : N, 15·9. $C_{16}H_{25}N_3$ requires N, 16·2%). The carbonate was formed as a white solid on exposure to air, and the *dihydrochloride* was precipitated as a gelatinous solid on addition of ether to a solution in ethanol. After being dried at 100°/12 mm., it had m. p. 272·5—273° (Found : N, 12·65. $C_{16}H_{25}N_3,2HCl$ requires N, 12·65%).

5-*Dimethylamino*-3-2′-*dimethylaminoethyl*-1 : 3-*diphenylpentan*-2-*one* (IV; R = ·CO·CH$_2$Ph).—The above cyanide (6·4 g.) in benzene (35 c.c.) was mixed with a Grignard solution made from benzyl chloride (10·2 g.), magnesium (2·1 g.), and ether (25 c.c.). The ether was distilled off and the residual solution vigorously refluxed for 22 hours. Excess of dilute hydrochloric acid was added and the mixture boiled for 3 hours. The benzene layer was removed and excess of ammonia added to the aqueous layer. The precipitated *base* (8·6 g., 99%), isolated by extraction with benzene and distillation, had b. p. 160°/0·01 mm., n_D^{25} 1·5444 (Found : N, 7·75. $C_{23}H_{32}ON_2$ requires N, 7·95%). The *dipicrate* formed a bright yellow crystalline powder, m. p. 175—176°, from acetone–ethyl acetate (Found : N, 14·05. $C_{35}H_{38}O_{15}N_8$ requires N, 13·85%). The dihydrochloride was not obtained crystalline.

Hydrogen Oxalates of 3-*Dialkylamino*-1-*phenylpropyl Cyanides*.—The 3-dimethylamino-compound (1·9 g.) and oxalic acid dihydrate (1·3 g.) in aqueous ethanol afforded the *hydrogen oxalate* (1·8 g.), m. p. 153° (Found : C, 60·4; H, 6·7. $C_{14}H_{18}O_4N_2$ requires C, 60·45; H, 6·5%). The 3-diethylamino-compound (2·2 g.) similarly afforded the *hydrogen oxalate* (2·3 g.), m. p. 168—171°, which formed flakes from ethanol–acetone (Found : C, 62·8; H, 7·2. $C_{16}H_{22}O_4N_2$ requires C, 62·75; H, 7·2%).

Attempted Ketonisation of 3-*Dialkylamino*-1-*phenylpropyl Cyanides*.—The 3-dimethylamino-compound (9·4 g.) in benzene (24 c.c.) was vigorously boiled for 4 hours with a Grignard solution made from methyl iodide (15·6 g.), magnesium (2·9 g.), and ether (20 c.c.). The basic product was unchanged cyanide (7·25 g., 71%), b. p. 98—103°/0·5 mm., n_D^{20} 1·5081, identified by conversion into the hydrogen oxalate, m. p. 153° (4·55 g. from 5·6 g. of base). In a similar experiment, 3-diethylamino-1-phenylpropyl cyanide was recovered unchanged in 68% yield, and there was again no evidence of ketonisation.

Reaction of 1 : 1-*Diphenylacetone with* 2-*Dimethylaminoethyl Chloride*.—The ketone (10·5 g.), dry benzene (30 c.c.), and sodamide (2·5 g.) were stirred at 35—45° for 30 minutes. 2-Dimethylaminoethyl chloride (5·4 g.) in benzene (10 c.c.) was added and the mixture heated slowly to boiling. After 2 hours' refluxing, the mixture was extracted with dilute hydrochloric acid to afford unchanged 1 : 1-diphenylacetone (7·7 g., 73%), m. p. 58·5—60·5°, and a basic fraction (1·8 g.), b. p. 136—145°/0·15 mm. The latter gave a gummy hydrochloride which was repeatedly recrystallised from *iso*propanol–ether, to give 5-dimethylamino-3 : 3-diphenylpentan-2-one hydrochloride (0·45 g., 3%), m. p. 182—184°, not depressed on admixture with an authentic specimen (following experiment). The hydrochloride (0·25 g.) was converted into the free base and added to toluene-*p*-sulphonic acid (0·15 g.) in *iso*propanol ether. The resulting *toluene*-p-*sulphonate* (0·2 g.) formed solvated prisms, m. p. 89—90°, which had m. p. 109·5—110° after being dried at 80°/15 mm. (Found : N, 2·9. $C_{26}H_{31}O_4NS$ requires N, 3·8%). This was identical with the toluene-*p*-sulphonate prepared in the following experiment.

5-*Dimethylamino*-3 : 3-*diphenylpentan*-2-*one* (VI).—The base was prepared from the corresponding cyanide and methylmagnesium iodide (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 510). The hydrochloride formed white prisms, m. p. 182·5—184° (Dupré *et al.* give m. p. 186—187·5°; Walton, Ofner, and Thorpe, *J.*, 1949, 654, give m. p. 152—153°). The toluene-*p*-sulphonate (0·45 g. from 0·4 g. of base) formed solvated prisms, m. p. 90·5—92°, from acetone–ether.

1 : 1-*Diphenylbutan*-2-*one*.—Diphenylacetic acid (106 g.) and thionyl chloride (43 c.c.) were refluxed for 4 hours. The fraction of b. p. 158—170°/4·5 mm. (101 g., 88%) gave pure diphenylacetyl chloride, m. p. 54—56°, on trituration with light petroleum (b. p. 40—60°). The acid chloride (18·4 g.) in benzene (115 c.c.) was added to a solution of diethylcadmium prepared in the usual way from ethyl bromide (10·9 g.), magnesium (2·7 g.), ether (100 c.c.), and anhydrous cadmium chloride (9·2 g.). The ether was distilled off and the residual benzene suspension refluxed for 3 hours. The mixture was decomposed with dilute hydrochloric acid and fractionated to yield 1 : 1-diphenylbutan-2-one (9·8 g., 56%), b. p. 175—180°/5 mm. (semicarbazone, m. p. 185°), and (non-volatile) diphenylacetic anhydride (6·25 g., 39%), colourless

needles, m. p. 100° (from methanol), converted by aqueous ammonia into diphenylacetamide, m. p. 168·5—169·5°.

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