200. *Heterocyclic Ketones. Part II. β-Amino-ketones containing Thiophen, Thiazole, and Furan Nuclei, and their Behaviour towards Phenylhydrazine.*

By G. A. Levvy and Hugh B. Nisbet.

The syntheses of β-amino-ketones of the type $R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR_2,HCl$ from 2-acetylthiophen, 2-acetyl-4-phenylthiazole, and 2-acetylfuran by the Mannich reaction are described. The thiophen derivatives have some local anæsthetic action and the other compounds have been prepared for pharmacological tests.

In attempts to prepare phenylhydrazones from a series of β-amino-ketones (III; $NR_2 = NMe_2$, NEt_2, NPr_2, or NC_5H_{10}) an identical compound was obtained from all four sources. It is suggested that this is 1-*phenyl*-3-(4′-*phenyl*-2′-*thiazolyl*)*pyrazoline* (V) and evidence is given in support of this constitution.

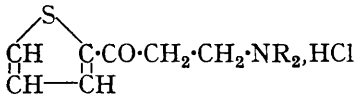
β-Aminoethyl ketones may be obtained from methyl ketones by condensation with formaldehyde and hydrochlorides of secondary bases:

$$R{\cdot}CO{\cdot}CH_3 + CH_2O + NHR'_2,HCl \longrightarrow (I)\ R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR'_2,HCl + H_2O$$

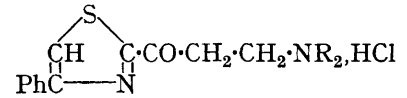
Mannich and his co-workers (*Ber.*, 1920, **53**, 1368; *Arch. Pharm.*, 1927, **265**, 589) have prepared compounds of type (I) from a large number of saturated and unsaturated ketones. Blicke and Blake (*J. Amer. Chem. Soc.*, 1930, **52**, 235) have applied this reaction to 2-acetylpyrrole. In Part I (Nisbet and Gray, J., 1933, 839), it was shown that β-amino-ketones of this type could be obtained from furfurylideneacetone by the Mannich reaction. This has now been extended to the preparation of β-amino-ketones derived from 2-acetylthiophen, 2-acetyl-4-phenylthiazole, and 2-acetylfuran.

From 2-acetylthiophen, *2-thienyl β-piperidinoethyl ketone* and *2-thienyl β-dimethylaminoethyl ketone* have been prepared as hydrochlorides (II).

2-Acetyl-4-phenylthiazole was used as the starting material for the preparation of compounds of this type in the thiazole series owing to the difficulty of obtaining thiazole derivatives unsubstituted at position 4. The ketone was obtained by the method of Olin and Johnson (*J. Amer. Chem. Soc.*, 1931, **53**, 1473) and, in its condensations with formaldehyde and secondary base hydrochlorides, it was found necessary to have free hydrochloric acid present and to heat for a considerably longer period than is usually necessary in this type of reaction. *4-Phenyl-2-thiazolyl β-piperidino-, β-dimethylamino-, β-diethylamino-,* and *β-di-n-propylamino-ethyl ketone hydrochlorides* (III) have been prepared. No reaction was observed with di-*n*-butylamine hydrochloride or with diethanolamine hydrochloride.

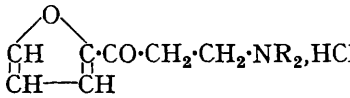


(II; $NR_2 = NC_5H_{10}$ or NMe_2.)

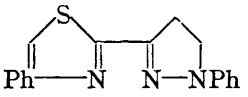


(III; $NR_2 = NC_5H_{10}$, NMe_2, NEt_2, or NPr_2.)

2-Acetylfuran and formaldehyde have been condensed with piperidine, dimethylamine, di-*n*-propylamine, di-*n*-butylamine, and di-(β-hydroxyethyl)amine hydrochlorides to give the corresponding *2-furyl β-dialkylaminoethyl ketone hydrochlorides* (IV). The analogous



[IV; $NR_2 = NC_5H_{10}$, NMe_2, NPr_2, NBu_2, or $N(CH_2{\cdot}CH_2{\cdot}OH)_2$.]



(V.)

diethylamino-compound could not be obtained under exactly similar conditions to those used for the other condensations. The behaviour of diethylamine in this type of reaction appears to be erratic, for the above observation is in agreement with that of Kermack and Muir (J., 1931, 3091) that no condensation occurs between methyl ethyl ketone, formaldehyde, and diethylamine hydrochloride, and our own further observation that

the analogous reaction with acetophenone also fails. A diethylamino-derivative, however, has been obtained in the 2-acetyl-4-phenylthiazole series and in the condensation with anisylideneacetone to be described shortly in connection with other work.

The physiological properties of the two thiophen derivatives have been examined (Sinha, Ph.D. Thesis, Edinburgh University, 1936). Although they both show local anæsthetic action, it is considerably less than that of cocaine. The other new amino-ketones are to undergo pharmacological tests with a view to determining, if possible, the effect of varying the size of the dialkylamino-part of the molecule.

Mannich and Bauroth (*Ber.*, 1924, **57**, 1108) have noted the formation of 1-phenyl-pyrazoline-3-propionic acid as the phenylhydrazide by the action of phenylhydrazine at 100° on 4-keto-6-dimethylaminohexoic acid hydrochloride, and Jacob and Madinaveitia (J., 1937, 1929) have described the formation of 1 : 3-diphenylpyrazoline and 1-phenyl-3-methylpyrazoline by the action of phenylhydrazine on phenyl β-dimethylaminoethyl ketone and methyl β-dimethylaminoethyl ketone respectively.

The treatment of 4-phenyl-2-thiazolyl β-dialkylaminoethyl ketone hydrochlorides (III; $NR_2 = NC_5H_{10}$, NMe_2, NEt_2, or NPr_2) with phenylhydrazine yields, instead of the phenylhydrazones expected, a compound, m. p. 198°, identical from all four sources, containing no halogen, and showing a strong green fluorescence in solution. In the light of the reactions noted above, it is suggested that the compound is 1-*phenyl*-3-(4′-*phenyl*-2′-*thiazolyl*)*pyrazoline* (V). A dark blue colour is obtained in Knorr's test for pyrazolines (*Annalen*, 1887, **238**, 200). Fluorescence in solution is reversibly destroyed by mineral acid.

The lability of dialkylamino-groups in this degradation is, therefore, apparently independent of the type of ketone, and, at least in the thiazolyl series studied, of the size of the dialkylamino-radical (R). In fact, in the latter case, the pyrazoline was obtained in better yield from the diethyl- and di-*n*-propyl-amino-ketones than from the dimethyl-amino-ketone. The conditions used in the preparation of the pyrazoline were much less vigorous than those obtaining in the papers cited above.

There is some evidence for the reversibility of the Mannich reaction (J., 1931, 3089) used in the preparation of the dialkylamino-ketones, and the analytical figures for the pyrazoline differ little from those required for the *phenylhydrazone* of 2-acetyl-4-phenylthiazole, which might conceivably be formed by such reversal. The latter, however, has been prepared for purposes of comparison and found to melt at 141°. Olin and Johnson (*J. Amer. Chem. Soc.*, 1931, **53**, 1473) described a phenylhydrazone, m. p. 208—209°, but record no analysis. The *acetyl* derivative of our compound has this m. p., suggesting that, under the conditions used in the preparation of the phenylhydrazone by Olin and Johnson, acetylation occurred.

The action of phenylhydrazine on β-dialkylaminoethyl ketones derived from 2-acetylfuran and 2-acetylthiophen has been studied, but no product has been isolated in any case.

Experimental.

2-*Thienyl* β-*Piperidinoethyl Ketone Hydrochloride*.—2-Acetylthiophen (0·05 g.-mol.), piperidine hydrochloride (0·05 g.-mol.), and paraformaldehyde (1·5 g.) in absolute alcohol (5 c.c.) were refluxed for 15 minutes. Another portion of paraformaldehyde (1·5 g.) was added, and heating continued 15 minutes longer. The solid obtained on cooling crystallised from alcohol in white leaflets, m. p. 199° (Found: N, 5·4. $C_{12}H_{17}ONS,HCl$ requires N, 5·4%).

2-*Thienyl* β-*dimethylaminoethyl ketone hydrochloride*, the preparation of which was carried out as in the case of the piperidino-compound, formed white plates, m. p. 172° (Found: N, 6·9; Cl, 15·6. $C_9H_{13}ONS,HCl$ requires N, 6·8; Cl, 16·2%).

ω-*Bromoacetophenone*.—For the synthesis of 2-acetyl-4-phenylthiazole (see below) large quantities of ω-bromoacetophenone were required. The methods given in the literature did not always yield a satisfactory product. The following modification gave excellent results. To acetophenone (20 g.) in glacial acetic acid (100 c.c.), bromine (9 c.c.) was added dropwise, with constant shaking. After 20 minutes the solution suddenly lightened in colour. It was immediately poured into a large quantity of ice-water containing a little sodium carbonate, and kept overnight. The white crystals which separated were recrystallised from 95%

alcohol. When large quantities are required, small portions may be treated as above in serial fashion. Yield, 80%; m. p. 50°.

4-Phenyl-2-thiazolyl β-Piperidinoethyl Ketone Hydrochloride.—2-Acetyl-4-phenylthiazole (0·05 g.-mol.; prepared by the method of Olin and Johnson, *loc. cit.**) and piperidine hydrochloride (0·05 g.-mol.) were dissolved in absolute alcohol (20 c.c.) containing concentrated hydrochloric acid (1 c.c.), paraformaldehyde (1·5 g.) added, and the mixture refluxed until homogeneous. After the addition of another portion of formaldehyde (0·75 g.), boiling was continued for 3 hours. The white solid which separated on cooling was washed with ether and crystallised from alcohol; m. p. 193—195° (decomp.) (Found: C, 60·7, 60·3; H, 6·2, 6·1. $C_{17}H_{20}ON_2S$,HCl requires C, 60·5; H, 6·2%).

The other β-amino-ketones derived from 2-acetyl-4-phenylthiazole were prepared in the same manner, the only variation in each case being in the time of heating. *4-Phenyl-2-thiazolyl β-dimethylaminoethyl ketone hydrochloride* (4 hours) crystallised from alcohol in white platelets, m. p. 174° (Found: C, 56·35; H, 5·45. $C_{14}H_{16}ON_2S$,HCl requires C, 56·6; H, 5·7%). *4-Phenyl-2-thiazolyl β-diethylaminoethyl ketone hydrochloride* (9 hours) was obtained as a white amorphous solid, which was crystallised from alcohol; m. p. 142° (Found: C, 59·0; H, 6·5. $C_{16}H_{20}ON_2S$,HCl requires C, 59·1; H, 6·5%). *4-Phenyl-2-thiazolyl β-di-n-propylaminoethyl ketone hydrochloride* (12 hours), a pale yellow, amorphous solid, decomposed over a large range of temperature (Found: C, 61·4; H, 7·1. $C_{18}H_{24}ON_2S$,HCl requires C, 61·2; H, 7·1%).

2-Furyl β-Piperidinoethyl Ketone Hydrochloride.—2-Acetylfuran (0·05 g.-mol.), piperidine hydrochloride (0·05 g.-mol.), and paraformaldehyde (1·5 g.) in absolute alcohol (20 c.c.) were heated under reflux for 15 minutes. Thereafter a second portion of paraformaldehyde (0·75 g.) was added, and heating continued for 15 minutes. The white solid which separated on cooling was washed with ether and crystallised from water, forming leaflets, m. p. 185—186° (Found: C, 58·9; H, 7·5; N, 6·2. $C_{12}H_{17}O_2N$,HCl requires C, 59·0; H, 7·4; N, 5·75%).

2-Furyl β-Dimethylaminoethyl Ketone Hydrochloride.—A few drops of concentrated hydrochloric acid were added to a mixture of 2-acetylfuran, dimethylamine hydrochloride, and paraformaldehyde (0·05 g.-molar quantities) in absolute alcohol (15 c.c.). The whole was boiled under reflux for 15 minutes, and again, after addition of a second portion of formaldehyde (0·75 g.), for 30 minutes. The solid which separated on cooling crystallised from water in white leaflets, m. p. 178° (Found: C, 52·9; H, 7·2; N, 7·0. $C_9H_{13}O_2N$,HCl requires C, 52·9; H, 6·9; N, 6·9%).

2-Furyl β-di-n-propylaminoethyl ketone hydrochloride, similarly prepared from 2-acetylfuran (0·03 g.-mol.), di-*n*-propylamine hydrochloride (0·03 g.-mol.), and paraformaldehyde (1 g.) in absolute alcohol (7·5 c.c.) containing a few drops of concentrated hydrochloric acid, the periods of heating being 15 minutes before, and 45 minutes after, the addition of more paraformaldehyde (0·5 g.), crystallised on cooling and a second crop was obtained on evaporation of the mother-liquor. Recrystallisation from alcohol gave white cubes, decomp. 129—130° (Found: C, 60·0; H, 8·6; N, 5·3. $C_{13}H_{21}O_2N$,HCl requires C, 60·0; H, 8·5; N, 5·4%).

2-Furyl β-di-n-butylaminoethyl ketone hydrochloride was prepared by refluxing a solution of 2-acetylfuran (0·05 g.-mol.), di-*n*-butylamine hydrochloride (0·05 g.-mol.), and paraformaldehyde (1·5 g.) in absolute alcohol (15 c.c.) containing a few drops of concentrated hydrochloric acid for 15 minutes, and again for 1 hour after the addition of another portion of paraformaldehyde. When the solution was evaporated to half its volume on the steam-bath and cooled, white crystals separated. The compound was recrystallised from alcohol; m. p. 111° (Found: C, 62·3; H, 9·3. $C_{15}H_{25}O_2N$,HCl requires C, 62·5; H, 9·0%).

2-Furyl β-Di-(β-hydroxyethyl)aminoethyl Ketone Hydrochloride.—The viscous oil obtained by evaporating a solution of diethanolamine (5·3 g.) neutralised with hydrochloric acid was dissolved in absolute alcohol (20 c.c.), and 2-acetylfuran (5·5 g.), paraformaldehyde (1·5 g.), and concentrated hydrochloric acid (0·5 c.c.) added. After heating under reflux for 15 minutes, a homogeneous solution was obtained. Heating was continued for 1 hour with the addition of a further quantity of paraformaldehyde (0·75 g.). The mixture was then evaporated on the steam-bath and kept in a vacuum over calcium chloride for several days. Prolonged vigorous stirring caused separation of the condensation *product*. This crystallised from alcohol in brown cubes, m. p. 100—101°, only slightly soluble in cold alcohol (Found: C, 50·1; H, 7·0; N, 5·5. $C_{11}H_{17}O_4N$,HCl requires C, 50·0; H, 6·8; N, 5·3%).

1-Phenyl-3-(4′-phenyl-2′-thiazolyl)pyrazoline.—To any one of the 4-phenyl-2-thiazolyl

* In the preparation from benzoyl chloride, acetaldehyde, and potassium cyanide of benzoyllactonitrile used in this synthesis, addition of ice must be continued as this disappears during the course of the reaction (private communication from T. B. Johnson).

β-dialkylaminoethyl ketone hydrochlorides mentioned above, in the minimum quantity of cold absolute alcohol necessary for solution, was added an equivalent weight of phenylhydrazine and the same amount of glacial acetic acid. The yellow needles which separated overnight were recrystallised from absolute alcohol; m. p. 198° after sintering at 190°; identical by mixed m. p. from all four sources. The *pyrazoline* was not very soluble in organic solvents (Found: C, 70·5; H, 5·0; N, 14·0. $C_{18}H_{15}N_3S$ requires C, 70·8; H, 4·9; N, 13·8%).

Phenylhydrazone of 2-Acetyl-4-phenylthiazole.—The ketone was treated with an equivalent weight of phenylhydrazine and a weight of glacial acetic acid equal to that of the latter, in cold absolute alcohol. The *phenylhydrazone* separated almost immediately. It crystallised from absolute alcohol in yellow prisms, m. p. 141°, fairly readily soluble in hot solvents (Found: C, 69·35, 69·45; H, 4·9, 5·0. $C_{17}H_{15}N_3S$ requires C, 69·6; H, 5·1%).

When acetyl chloride was dropped into a cold benzene solution of the phenylhydrazone, the N-*acetyl* derivative separated as a brick-red solid. Crystallisation from absolute alcohol gave pale yellow cubes, m. p. 209° (Found: C, 69·7; H, 5·4; N, 13·9, 13·8. $C_{18}H_{17}N_3S$ requires C, 70·4; H, 5·5; N, 13·7%).

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HERIOT-WATT COLLEGE, EDINBURGH. [*Received, May 12th,* 1938.]