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α-CHLORO-ENAMINES—IV

AMINATED HETEROCYCLES FROM THE REACTION OF PHOSGENE WITH SUBSTITUTED ACETAMIDES

R. BUYLE and H. G. VIEHE

Union Carbide European Research Associates, s.a., 95 rue Gatti de Gamond, Brussels 18, Belgium

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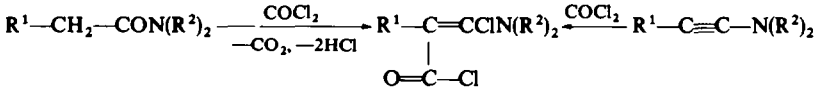
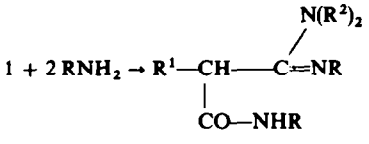
Abstract—β-Chlorocarbonyl-α-chloro-enamines are easily available derivatives of malonic acid. They have two reactive Cl atoms and condense with bis-nucleophiles, such as hydrazines, hydroxylamines, amidines, ureas, *o*-phenylenediamines and *o*-aminothiophenol to form new dialkylaminosubstituted 5-, 6- and 7-membered heterocycles.

IN PRECEDING publications,[1] it has been shown that N,N-dialkyl-substituted acetamides or their corresponding ynamines form with phosgene β-chlorocarbonyl-α-chloro-enamines (I) as reactive derivatives of the malonic acid series:



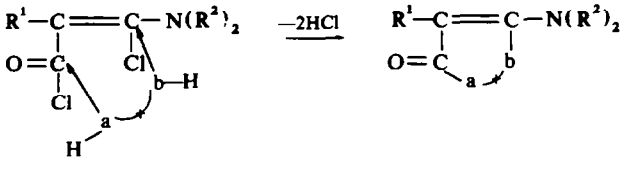
I

Both Cl atoms become successively substituted with nucleophiles such as amines[2] which form β-amido-amidines (II):



II

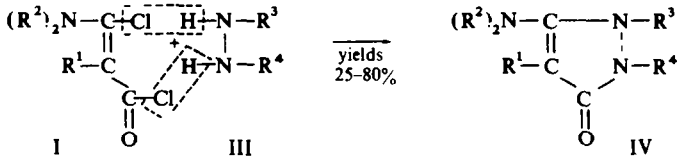
It has been mentioned,[3] that I with various bis-nucleophiles yields many new heterocyclic compounds. We now describe some typical examples of this reaction:



Treatment at room temperature, of I with one mol equiv. of a bis-nucleophile and two mol equiv. of the appropriate base in an aprotic solvent affords the amino substituted heterocycle:

1. *Reactions with hydrazine derivatives* (III) *to 3-dialkylamino-5-pyrazolones*[4] IV

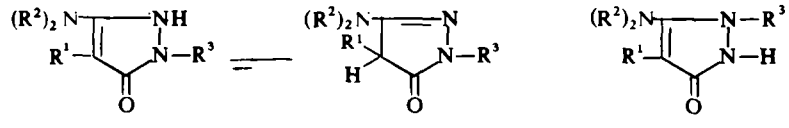
The simplest case of this synthesis of pyrazolones IV is realized with symmetrically disubstituted hydrazine III i.e., with $R^3 = R^4$



I III IV

IV a: R^1 = Me; $(R^2)_2$ = —$(CH_2)_5$—; $R^3 = R^4$ = Ph
b: R^1 = Cl; R^2 = C_2H_5; $R^3 = R^4$ = Ph
c*: R^1 = Me; $(R^2)_2$ = —$(CH_2)_5$—; $R^3 = R^4$ = H

With mono-substituted hydrazines the expected two isomeric pyrazolones V and VI can be isolated and recognized by their different NMR spectra especially by the NH signals present only in VI since the tautomeric form V_1 is less favored than V.



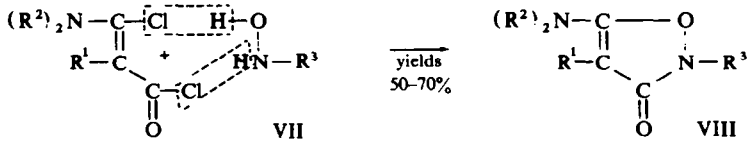
V_1 V VI

V and VI a: R^1 = Et, R^2 = Me, R^3 = Me
b. R^1 = Et, R^2 = Et, R^3 = Me
c: R^1 = Et, R^2 = Et, R^3 = Ph

Methyl and phenylhydrazine have been used for condensations with I: the former produced predominantly isomer V and the latter mainly VI. This result is expected[5] because of the higher reactivity of chlorine on the carbonyl group[6] and because of the higher reactivity of the methyl substituted nitrogen.

2. *Reactions with* N-*substituted hydroxylamines* VII *to* 5-*dialkylamino*-3-*isoxazolones* VIII

Both N-methyl and N-phenylhydroxylamine give only 3-isoxazolones (VIII)



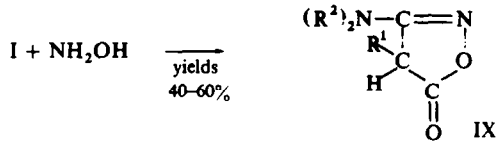
VII VIII

I

VIII a: R^1 = Me, $(R^2)_2$ = —$(CH_2)_5$—, R^3 = Me
b: R^1 = Et, R^2 = Et, R^3 = Ph
c: R^1 = Me, $(R^2)_2$ = —$(CH_2)_5$—, R^3 = Ph

IR absorption bands (cm^{-1}) in KBr: 1·635 vs, 1·705 w.

* The tautomeric structure V (R^3 = H) is predominant for IVc.



IX a: R^1 = Et, R^2 = Et
b: R^1 = Me, $(R^2)_2$ = —$(CH_2)_5$—

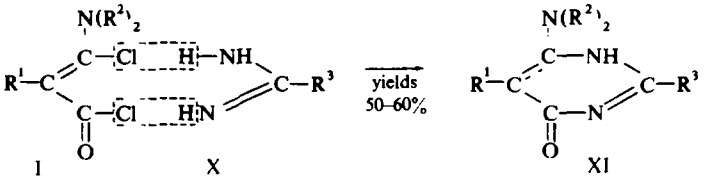
IR absorption band (cm^{-1}) in KBr: 1·772s.

whereas with hydroxylamine itself 5-isoxazolones (IX) are formed exclusively. This structure correlation is based on their characteristically different IR spectra[7] as formulated.

For IX results a further structure proof from the NMR spectrum which rules out isomer VIII because of the missing NH signal.

3. *Reactions with amidines* X *to 6-dialkylamino-4-pyrimidinones* (XI)

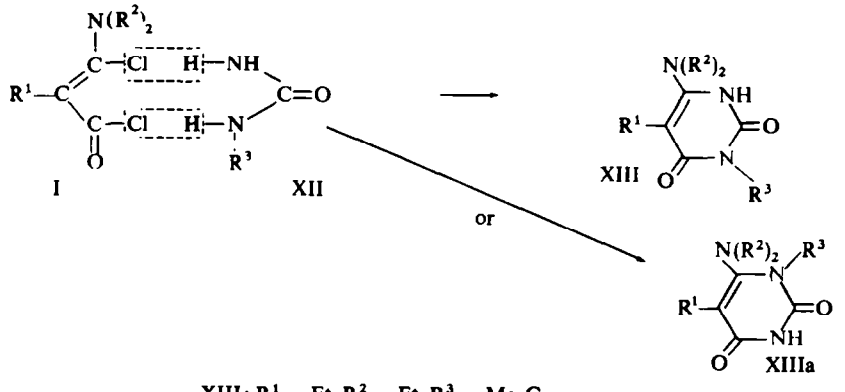
Benzamidine X (R^3 = Ph) leads with I to 6-dialkylamino-4-pyrimidinones XI:



XI a: R^1 = Me, $(R^2)_2$ = —$(CH_2)_5$—, R^3 = Ph
b: R^1 = Et, R^2 = Et, R^3 = Ph

4. *Reactions with urea derivatives* XII *to 4-dialkylamino-2,6-dioxopyrimidines* (XIII)

So far only t-butylurea has been tried for this reaction producing exclusively one type of isomer (XIII or XIIIa).

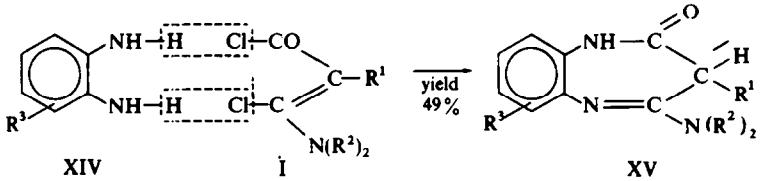


XIII: R^1 = Et, R^2 = Et, R^3 = Me_3C

If as in the other ambident reactions of I described above, the better nucleophile attacks preferentially the chlorine of the carbonyl group, the obtained product should have structure XIII.

5. *Reactions with* o-*phenylenediamines to* 4-*dialkylamino*-1,5-*benzodiazepin*-2-*one* (XV)

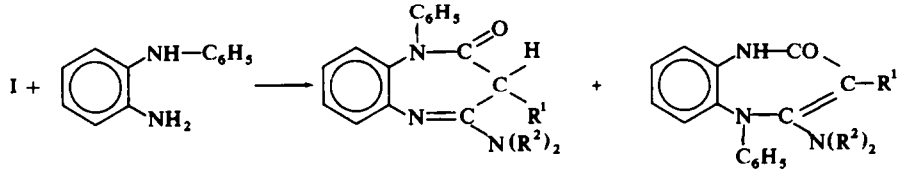
The foregoing reactions of I to 5- and 6-membered heterocycles left to be expected that 7-membered ring systems would result from 1,4-bis-nucleophiles. In fact *o*-phenylenediamines have been found to react accordingly. Thus with *o*-phenylenediamines (XIV) yields of 45–65% of 1,5-benzodiazepin-2-ones (XV) have been isolated.



XIV I XV

XV a: R^1 = Me $(R^2)_2$ = —$(CH_2)_5$— R^3 = H
b: R^1 = Et R^2 = Et R^3 = H
c: R^1 = Ph R^2 = Et R^3 = H
d: R^1 = Et R^2 = Et R^3 = Cl

N-phenyl-*o*-phenylenediamine yields the two isomers XVI and XVII of which the latter one predominates as confirmed by NMR studies.

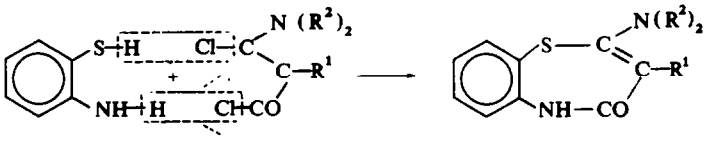


XVI XVII

XVI and XVII: R^1 = Me, $(R^2)_2$ = —$(CH_2)_5$—

6. *Reactions with* o-*aminothiophenol to* 2-*dialkylamino*-1,5-*benzothiazepin*-4-*one* XVIII

o-Aminothiophenol reacts with I to yield 1,5-benzothiazepin-4-one (XVIII).[8]



I XVIII

XVIII: R^1 = Me, $(R^2)_2$ = —$(CH_2)_5$—

EXPERIMENTAL*

M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 21 spectrometer. Varian Associates Model A60 was used for NMR spectra with TMS as internal standard (chemical shifts given in τ).

3-*Dialkylamino-pyrazolin-5-ones* (IV, V and VI)

A soln of I (0·02 mole) in ether (75 ml) was stirred at 0° while III (0·06 mole) in CH_2Cl_2 (100 ml) was added dropwise over a period of 30 min.

* With W. Rennerts and J. Eloy.

The soln was allowed to warm up to room temp and was then stirred for 10 hr. The ppt of III hydrochloride was filtered off and the organic phase evaporated under reduced press.

The oily residue was extracted with hexane (150 ml). Evaporation of this soln gave a liquid which was fractionated to give V. Crystallization of the hexane insoluble material gave IV or VI.

1,2-Diphenyl-3-piperidyl-4-methyl pyrazolin-5-one (IVa), in 60% yield from EtOH, m.p. 149°, $\lambda(cm^{-1})$ 1690; 1635 in KBr pellet. (Found: C, 75·40; H, 6·94; N, 12·89; O, 4·99. Calc. for $C_{21}H_{23}N_3O$: C, 75·68; H, 6·91; N, 12·61; O, 4·80%).

1,2-Diphenyl-3-diethylamino-4-chloropyrazolin-5-one (IVb) in 25% yield from pet ether, m.p. 159°, $\lambda(cm^{-1})$ 1710, 1613 in KBr pellet. (Found: C, 66·91; H, 5·92; N, 12·19; O, 4·80. Calc. for $C_{19}H_{20}ClN_3O$: C, 66·78; H, 5·86; N, 12·30; O, 4·68%).

3-Piperidyl-4-methyl-2-pyrazolin-5-one (IVc) in 66% yield from EtOAc, m.p. 178°, $\lambda(cm^{-1})$ 1685, 1582 in KBr pellet. (Found: C, 60·00; H, 8·48; N, 23·58. Calc. for $C_9H_{15}N_3O$: C, 59·66; H, 8·29; N, 23·21%).

1-Methyl-3-dimethylamino-4-ethyl-2-pyrazolin-5-one (Va) in 62% yield, b.p. 83° (0·4 mm), $\lambda(cm^{-1})$ 1681, 1580 on the pure liquid. (Found: C, 56·63; H, 8·86; N, 25·21. Calc. for $C_8H_{15}N_3O$: C, 56·80; H, 8·87; N, 24·87%).

1-Methyl-3-diethylamino-4-ethyl-2-pyrazolin-5-one (Vb) in 70% yield, b.p. 97° (0·5 mm), $\lambda(cm^{-1})$ 1681, 1·580 on the pure liquid; NMR (τ): 6·7/M/1H in $CDCl_3$. (Found: C, 60·38; H, 9·90; N, 21·75. Calc. for $C_{10}H_{19}N_3O$: C, 60·90; H, 9·65; N, 21·32%).

1-Phenyl-3-diethylamino-4-ethyl-2-pyrazolin-5-one (Vc) in 27% yield, b.p. 142° (0·01 mm), $\lambda(cm^{-1})$ 1687, 1580 on the pure liquid. (Found: C, 69·14; H, 8·32; N, 16·78. Calc for $C_{15}H_{21}N_3O$: C, 69·50; H, 8·11; N, 16·21%).

2-Methyl-3-dimethylamino-4-ethyl-3-pyrazolin-5-one (VIa) in 9% yield from hexane, m.p. 148°, $\lambda(cm^{-1})$ 1592, 1535 in KBr pellet. (Found: C, 56·48; H, 8·96; N, 25·11. Calc. for $C_8H_{15}N_3O$: C, 56·80; H, 8·87; N, 24·87%).

2-Methyl-3-diethylamino-4-ethyl-3-pyrazolin-5-one (VIb) in 11% yield from pet ether, m.p. 161°. $\lambda(cm^{-1})$ 1600, 1535 in KBr pellet. (Found: C, 60·71; H, 9·78; N, 21·27. Calc. for $C_{10}H_{19}N_3O$: C, 60·90; H, 9·65; N, 21·32%).

2-Phenyl-3-diethylamino-4-ethyl-3-pyrazolin-5-one (VIc) in 42% yield from EtOH, m.p. 169°. $\lambda(cm^{-1})$ 1610, 1535 in KBr pellet; NMR (τ): −0·3/S/1H in $CDCl_3$. (Found: C, 69·20; H, 8·29; N, 16·34. Calc. for $C_{15}H_{21}N_3O$: C, 69·50; H, 8·11; N, 16·21%).

5-Dialkylamino isoxazolin-3-ones (VIII a–c)

To a soln containing 0·02 mole of I in 100 ml CH_2Cl_2 0·06 mole of substituted VII in 100 ml CH_2Cl_2 were added during 30 min with stirring and cooling in an ice bath.

After stirring for 10 hr at room temp the ppt of VII hydrochloride was filtered off and the organic phase evaporated under reduced press.

The residue was treated with EtOAc (150 ml) and then filtered to give another fraction of VII hydrochloride. Evaporation of the solvent at reduced press yielded a yellow-brown oily residue. The latter was distilled or triturated with 50 ml hexane to give VIII.

2,4-Dimethyl-5-piperidyl isoxazolin-3-one (VIIIa) in 69% yield, b.p. 124° (0·05 mm), $\lambda(cm^{-1})$ 1675 w, 1612 v.s. on the pure liquid. (Found: C, 60·25; H, 8·21; N, 14·59. Calc. for $C_{10}H_{16}N_2O_2$: C, 61·25; H, 8·16; N, 14·28%).

2-Phenyl-4-ethyl-5-diethylamino isoxazolin-3-one (VIIIb) in 54% yield from EtOAc–hexane, m.p. 128°, $\lambda(cm^{-1})$ 1672 w, 1617 v.s. in KBr pellet. (Found: C, 69·22; H, 7·95; N, 10·74; O, 12·52. Calc. for $C_{15}H_{20}N_2O_2$: C, 69·22; H, 7·69; N, 10·77; O, 12·32%).

2-Phenyl-4-methyl-5-piperidyl isoxazolin-3-one (VIIIc) in 57% yield from hexane, m.p. 78°, $\lambda(cm^{-1})$ 1692 w, 1635 v.s. in KBr pellet. (Found: C, 69·89; H, 7·26; N, 10·88; O, 12·31. Calc. for $C_{15}H_{18}N_2O_2$: C, 69·75; H, 6·98; N, 10·87; O, 12·40%).

3-Dialkylamino isoxazolin-5-ones IXa-b

A soln of 4·2 g (0·06 mole) hydroxylamine hydrochloride and 6·1 g (0·06 mole) Et_3N in 100 ml $CHCl_3$ was added dropwise to 0·02 mole of I in 100 ml CH_2Cl_2 over 30 min. The same procedure as described for the 3-isoxazolones was used after this addition.

3-Diethylamino-4-ethyl-2-isoxazolin-5-one (IXa) in 42% yield, b.p. 108° (0·05 mm), $\lambda(cm^{-1})$ 1772 s, 1570 s on the pure liquid; NMR (τ): 6·47/M/1H in CS_2. (Found: C, 58·13; H, 8·80; N, 15·42. Calc. for $C_9H_{16}N_2O_2$: C, 58·70; H, 8·69; N, 15·21%).

3-Piperidyl-4-methyl-2-isoxazolin-5-one (IXb) in 59% yield from pet ether, m.p. 49°, λ(cm^{-1}) 1780 s, 1578 s in KBr pellet. (Found: C, 58·62; H, 7·70; N, 15·52. Calc. for $C_9H_{14}N_2O_2$: C, 59·35; H, 7·69; N, 15·38%).

6-Dialkylamino-4-pyrimidinones XI a–b

To a stirred soln of 3·75 g (0·024 mole) benzamidine hydrochloride and 6·5 g (0·064 mole) Et_3N in 100 ml $CHCl_3$ was added dropwise 0·02 mole of I in 100 ml $CHCl_3$ soln over 30 min. The soln was then stirred at room temp for 10 hr. The hydrochloride salts were removed by filtration.

Evaporation of the mother liquid under vacuum yielded a semi-solid mass. The latter was triturated with 50 ml acetone and filtered to give the pyrimidinone XI.

2-Phenyl-5-methyl-6-piperidyl-4-pyrimidinone (XIa) in 59% yield from EtOH, m.p. 240°, λ(cm^{-1}) 1632 v.s. in KBr pellet. (Found: C, 70·99; H, 7·14; N, 15·78; O, 6·28. Calc. for $C_{16}H_{19}N_3O$: C, 71·38; H, 7·06; N, 15·61; O, 5·95%).

2-Phenyl-5-ethyl-6-diethylamino-4-pyrimidinone (XIb) in 51% yield from acetone, m.p. 141°. λ(cm^{-1}) 1632 v.s. in KBr pellet. (Found: C, 70·62; H, 7·98; N, 15·72; O, 6·12. Calc. for $C_{16}H_{21}N_3O$: C, 70·82; H, 7·75; N, 15·51; O, 5·92%).

O, 12·00%).

1-t-butyl-4-diethylamino-5-ethyl-2,6-dioxo1,2,5,6-tetrahydro pyrimidine (XIII)

To a stirred soln of 2·3 g (0·02 mole) t-butylurea and 4·1 g (0·04 mole) Et_3N in 100 ml CH_2Cl_2 was added dropwise 4·5 g (0·02 mole) of α-ethyl-β-chloro-β-diethylamino acrylyl chloride in 100 ml CH_2Cl_2. The soln was stirred at room temp for 10 hr. The $Et_3N \cdot HCl$ was removed by filtration. Evaporation of the mother liquid under vacuum yielded an oily residue which was extracted with hexane (200 ml).

After evaporation of the hexane soln the resulting residue was triturated with pet ether to give 2·8 g (37% yield) of XIII.

The analytical sample was recrystallized from hexane; m.p. 133°; λ(cm^{-1}) 1680, 1612, 1573 in KBr pellet. (Found: C, 62·21; H, 9·52; N, 15·86; O, 12·38. Calc. for $C_{14}H_{25}N_3O_2$: C, 62·90; H, 9·36; N, 15·74; O, 12·00%).

4-Dialkylamino-1,5-benzodiazepin-2-ones XVa–d, XVI *and* XVII

A. A soln of XIV (0·06 mole) in CH_2Cl_2 (100 ml) was stirred at 0° while I (0·02 mole) in CH_2Cl_2 (50 ml) was added dropwise.

B. A soln of XIV (0·02 mole) and Et_3N (0·04 mole) in CH_2Cl_2 (100 ml) was stirred at 0° while I (0·02 mole) in CH_2Cl_2 (50 ml) was added dropwise.

After the addition (case A and B) the ice bath was removed and the soln was allowed to warm to room temp and stirred for 10 hr. The hydrochloride salts were removed by filtration, and the solvent was evaporated *in vacuo*. The oily residue was extracted with EtOAc. The EtOAc extract was evaporated to a small volume. The addition of hexane gave XV.

1*H*-3-Methyl-4-piperidyl-2,3-dihydro-1,5-benzodiazepin-2-one (XVa), method A, in 53% yield from pet ether, m.p. 156°, λ (cm^{-1}), 1670 s, 1620 m, 1580 s in KBr pellet; NMR (τ): 6·11/M/1H; 9·06/D/3H; (J_{CH-CH_3} = 7 c/s) in C_6D_6. (Found: C, 70·22; H, 7·49; N, 16·11; O, 6·39. Calc. for $C_{15}H_{19}N_3O$: C, 70·03; H, 7·39; N, 16·35; O, 6·23%).

1*H*-3-Ethyl-4-diethylamino-2,3-dihydro-1,5-benzodiazepin-2-one (XVb), method A, in 65% yield from pet ether, m.p. 157°, λ (cm^{-1}) 1670 s, 1620 m, 1580 s in KBr pellet. (Found: C, 69·55; H, 8·36; N, 16·63. Calc. for $C_{15}H_{21}N_3O$: C, 69·50; H, 8·11; N, 16·21%).

1*H*-3-Phenyl-4-diethylamino-2,3-dihydro-1,5-benzodiazepin-2-one (XVc), method B, in 45% yield from EtOAc–hexane, m.p. 192° λ (cm^{-1}) 1670 s, 1620 m, 1580 s in KBr pellet. (Found: C, 73·89; H, 6·95; N, 13·70. Calc. for $C_{19}H_{21}N_3O$: C, 74·25; H, 6·84; N, 13·68%).

1*H*-3-Ethyl-4-diethylamino-2,3-dihydro-1,5-chlorobenzodiazepin-2-one (XVd), method B, in 56% yield from EtOAc, m.p. 136°, λ (cm^{-1}) 1680 s, 1610 m, 1570 s in KBr pellet. (Found: C, 61·45; H, 6·68; N, 14·35; Cl, 12·07. Calc. for $C_{15}H_{20}ClN_3O$: C, 61·30; H, 6·82; N, 14·32; Cl, 12·11%).

1-Phenyl-3-methyl-4-piperidyl-2,3-dihydro-1,5-benzodiazepin-2-one XVI, method B, the EtOAc extract was cooled to precipitate XVI in 7% yield, recrystallized from MeOH, m.p. 250°, λ (cm^{-1}) 1635 s, 1590 v.s. in KBr pellet. (Found: C, 75·28; H, 6·87; N, 12·64; O, 5·17. Calc. for $C_{21}H_{23}N_3O$: C, 75·68; H, 6·91; N, 12·61; O, 4·80%).

1*H*-3-Methyl-4-piperidyl-5-phenyl-1,5-benzodiazepin-2-one (XVII), method B, in 42% yield from hexane, m.p. 155° λ (cm^{-1}) 1625 m, 1595 s, 1570 m; NMR (τ): 8·05/S/3H in $CDCl_3$. (Found: C, 75·29; H, 6·91; N, 12·53; O, 4·71. Calc. for $C_{21}H_{23}N_3O$: C, 75·68; H, 6·91; N, 12·61; O, 4·80%).

2-Piperidyl-3-methyl-1,5-benzothiazepin 4 (5H) one (XVIII)

A soln of 2·5 g (0·02 mole) *o*-aminothiophenol in 100 ml pyridine was stirred at 0° while 4·5 g (0·02 mole) α-methyl-β-piperidyl acrylyl chloride in 50 ml CH_2Cl_2 was added dropwise.

The soln was allowed to warm to room temp and stirred for 10 hr. The hydrochloride salts were removed by filtration, and the solvents were evaporated *in vacuo*. The residue was extracted with ether. The ether extract was evaporated and the semi-solid residue triturated with a small amount of acetone to give 2·3 g (42% yield) of XVIII.

The analytical sample was recrystallized from EtOH, m.p. 184°, λ (cm^{-1}): 1645 v.s., 1580 s in KBr pellet. (Found: C, 65·88; H, 6·68; N, 10·31; S, 11·56. Calc. for $C_{15}H_{18}N_2OS$: C, 65·70; H, 6·57; N, 10·22; S, 11·67%).

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