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Synthesis and Reaction of 1-Substituted-4-benzylpiperazin-2-ones

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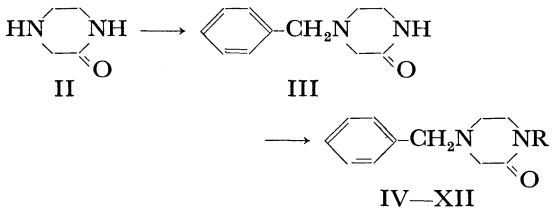
Introduction of a functional substituent at position 1 of 4-substituted piperazine-2-one (I) has been reported to be effected by two methods. Method A is an addition of I to an olefinic compound in the presence of base[1] or to an acetylenic compound at high temperature and pressure.[2] Method B is a reaction of sodium salt of I with an appropriate halide.[3]

However, the compounds thus prepared are quite few and are special types for practical application. In this note, preparation of 4-benzylpiperazin-2-ones (IV—XII) having a functional substituent at position 1 and their derivation and cyclization are described.

The starting material, piperazin-2-one (II), was prepared by Aspinall[4] by condensing ethyl chloroacetate with large excess of ethylenediamine, followed by cyclization. We found that the cyclization of the intermediate occurred during removal of excess of ethylenediamine at 100 °C instead of heating at 200 °C as described by Aspinall. 4-Benzylpiperazin-2-one (III) was readily available by reacting II with benzyl chloride.

Reaction conditions and yields in the preparation of IV—XII were tabulated in Table 1. In Table 2 were shown physical constants of the products and their salts respectively.



Reaction of ethyl 1-(4-benzyl-2-oxo)piperazinepropionate (VI) with concentrated ammonium hydroxide led to the formation of the corresponding amide (XIII) [mp 107—109 °C. Found: C, 64.25; H, 7.33; N, 16.01%. Calcd for $C_{14}H_{19}O_2N_3$: C, 64.34; H, 7.33; N, 16.08%]. Methyl 1-(4-benzyl-2-oxo)piperazinepropionate (V) and ethyl 1-(4-benzyl-2-oxo)piperazineacetate (XI) were allowed to react with hydrazine hydrate to give the corresponding hydrazides [V hydrazide was characterized as *m*-nitrobenzylidene derivative; mp 146—147 °C. Found: C, 61.82; H, 5.57; N, 17.17%. Calcd for $C_{21}H_{23}O_4N_5$: C, 61.60; H, 5.66; N, 17.11%. XI hydrazide; mp 108—109 °C. Found: C, 59.16; H, 6.87; N, 21.52%. Calcd for

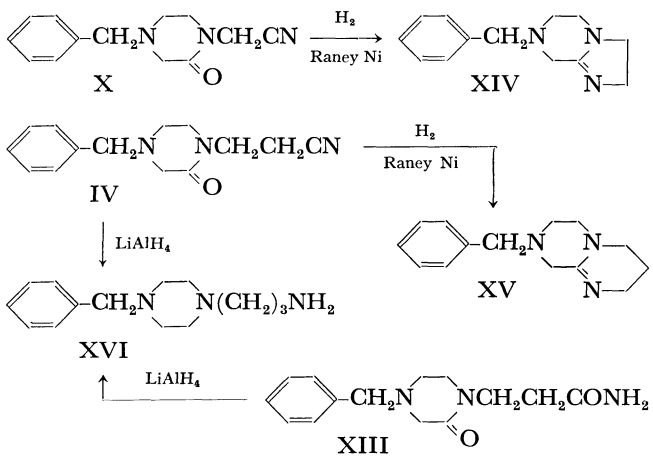
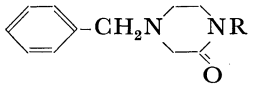


TABLE 1. PREPARATION OF 1-SUBSTITUTED-4-BENZYLPIPERAZIN-2-ONES



Compd. No.	R	Solvent	React. temp (°C)	Condition time (hr)	Yield (%)
IV	CH_2CH_2CN	CH_3CN	reflux	6	93
V	$CH_2CH_2COOCH_3$	Dioxane	90	8	68
VI	$CH_2CH_2COOC_2H_5$	Dioxane	reflux	6	90
VII	$CH_2CH_2CH_2CH_3$	Toluene	90	4	51
VIII[a]	$CH_2C_6H_5$	Toluene	90	2.5	54
IX	$CH_2CH_2N(C_2H_5)_2$	Toluene	90	5	60
X	CH_2CN	Toluene	r.t.	6.5	28
XI	$CH_2COOC_2H_5$	Toluene	90	5	66
XII	$CH_2CH=CH_2$	Toluene	93	5	51

a) Ref. 5

1) Rohm and Haas Co., Brit. 875135 (1961); *Chem. Abstr.*, **59**, 6420f (1963).
2) Rohm and Haas Co., Belg. 660617 (1965); *Chem. Abstr.*, **63**, 18119f (1965).
3) A. Sut, M. Podesta, and M. A. Lattes, *Chim. Ther.*, **1969**, 167; *Chem. Abstr.*, **71**, 91427z (1969).
4) S. R. Aspinall, *J. Amer. Chem. Soc.*, **62**, 1202 (1940).

Table 2. Physical constants of the products and their salts

Compd. No.	Bp (°C/mmHg)	Salt	Mp(°C)[b]
IV	205—206/1	picrate[c]	164—165
V	194—196/1	picrate[d]	129—130
VI	190—191/1	picrate[e]	111—112.5
VII	165—166/1	picrate[f]	113—115
VIII	205—207/1	HCl[g]	194—196
IX	186—188/1	picrate[h]	185—187
X[a]	185—186/1	picrate[c]	175—177
XI	191—193/1	HCl[h]	88—90
XII	159—160/1	picrate[c]	140—141

a) As semihydrate.
b) Melting points were measured on a hot plate stage and uncorrected.
Solvents for recrystallization.
c) C_2H_5OH.
d) CH_3OH–H_2O.
e) H_2O.
f) C_2H_5OH–$(C_2H_5)_2O$.
g) Dioxane.
h) CH_3CN–$(C_2H_5)_2O$.

$C_{13}H_{18}O_2N_4$: C, 59.52; H, 6.92; N, 21.36%].

Hydrogenation of 4-benzyl-1-cyanomethylpiperazin-2-one (X) and 4-benzyl-1-(2-cyanoethyl)piperazin-2-one (IV) in the presence of Raney nickel gave easily cyclized products, 7-benzyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazine (XIV) and 8-benzyl-2,3,6,7,8,9-hexahydro-4*H*-pyrazino[1,2-*a*]pyrimidine (XV) respectively. As an alternative route leading to the fused compound XV, selective reduction of nitrile group in IV or amide group in XIII was attempted using lithium aluminium hydride. However, the reduction of ring carbonyl group occurred simultaneously yielding 1-(3-aminopropyl)-4-benzylpiperazine (XVI) [bp 155—157 °C/1 mmHg. Picrate; mp 254—255 °C. Found: C, 41.92; H, 3.67; N, 17.64%. Calcd for $C_{32}H_{32}O_{21}N_{12}$ (tripicrate): C, 41.75; H, 3.50; N, 18.26%]. Hydrogenation of IV using 10% Pd–C in methanol containing hydrogen chloride was unsuccessful.

Experimental

4-Benzylpiperazin-2-one (III). A mixture of II(24.3 g), benzyl chloride(30.8 g) and sodium bicarbonate(24.5 g) in ethanol(300 ml) was gently refluxed for 5 hr. Upon cooling to room temperature, crystals of III separated out were collected by filtration. Concentration of the filtrate gave additional product. The combined crystals were recrystallized from benzene to give colorless prisms of III, mp 155—157 °C(lit,[6] mp 149—150 °C), 40.4 g (88%). Found: C, 69.50; H, 7.51; N, 14.89%. Calcd for $C_{11}H_{14}ON_2$: C, 69.44; H, 7.42; N, 14.73%.

4-Benzyl-1-(2-cyanoethyl)piperazin-2-one(IV) [*by Method A*]. A mixture of III(3.8 g), acrylonitrile(1.2 g) and powdered potassium hydroxide(20 mg) in acetonitrile(100 ml) was gently refluxed for 6 hr with stirring. The reaction mixture was concentrated, and to the residual oil was added 200 ml of ether. The ether insoluble substance was removed by filtration. The ethereal solution was concentrated and the residue was distilled under vacuum to obtaine 4.5 g of IV as a viscous pale yellow oil.

V and VI were prepared by this method.

*4-Benzyl-1-*n*-butylpiperazin-2-one(VII)* [*by Method B*]. A mixture of III(2.9 g) and finely pulverized sodium(0.35 g) in dry toluene(200 ml) was heated with vigorous stirring. At around 75 °C, III was completely dissolved and reaction mixture began to become turbid after 3 hr refluxing. After 7—8 hr refluxing the reaction mixture became gruel-like and all of the sodium was consumed. *n*-Butyl bromide(2.7 g) was added to the above mixture at room temperature. The mixture changed to a clear solution after 1 hr heating at 90 °C with stirring and additional 3 hr heating was continued. The reaction mixture was concentrated and ether(200 ml) was added to the oily residue. The ether-insoluble substance was removed by filtration and the ethereal solution was concentrated and then distilled under vacuum to give 1.9 g of VII as a viscous slightly yellow oil.

VIII-XII were prepared by this method.

*7-Benzyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazine (XIV).* X(4.0 g) in methanol(30 ml) containing ammonia(2 g) was hydrogenated at 95 °C in the presence of Raney nickel(1 g) and hydrogen at an initial pressure of 140 atm. The catalyst was removed by filtration and the filtrate was concentrated. The residue was distilled to give colorless oil of XIV, bp 176—179 °C/1 mmHg, 3.4 g(94%), hygroscopic. Found: C, 71.59; H, 8.13; N, 19.25%. (Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52%). IR(NaCl) cm^{-1}: 3350, 1635, 1492, 743, 701.

The picrate was recrystallized from acetonitrile, mp 197—199 °C. Found: C, 44.72; H, 3.50; N, 19.50%. Calcd for $C_{25}H_{23}O_{14}N_9$ (dipicrate): C, 44.58; H, 3.44; N, 18.71%.

*8-Benzyl-2,3,6,7,8,9-hexahydro-4H-pyrazino[1,2-*a*]pyrimidine (XV).* Hydrogenation of IV(6.1 g) by the same procedure as the preceding experiment gave colorless viscous oil of XV, bp 177—181 °C/1 mmHg, 5.5 g(96%), hygroscopic. Found: C, 72.24; H, 8.57; N, 18.28%. (Calcd for $C_{14}H_{19}N_3$: C, 73.32; H, 8.35; N, 18.33%). IR(NaCl) cm^{-1}: 3300, 1643, 1495, 750, 705. Picrate: mp 193—195 °C(methanol). Found: C, 45.33; H, 3.67; N, 18.25%. Calcd for $C_{26}H_{25}O_{14}N_9$(dipicrate): C, 45.42; H, 3.67; N, 18.34%.

5) W. B. Martin, Jr. and A. E. Martell, *J. Amer. Chem. Soc.*, **72**, 4301 (1950).

6) H. S. Mosher, J. Cornell, Jr., O. L. Stafford, and T. Roe, Jr., *ibid.*, **75**, 4949 (1953).