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Reaction of N-Haloamide. XVI.[1] Reaction of N,N-Dichlorophenylacetamide with Aliphatic Secondary Amines

Hiromi Terauchi, Shoji Takemura, and Yoshio Ueno

Faculty of pharmaceutical Sciences, Kinki University[2]

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Secondary amines such as diethylamine (II), piperidine (IV), and 2-ethylpiperidine (VI) were allowed to react with N,N-dichlorophenylacetamide (I) to give N,N-diethyl-N'-benzylurea (III), benzylcarbamoylpiperidine (V), and benzylcarbamoyl-2-ethylpiperidine (VII), respectively.

Three moles of amines were consumed to complete the reactions, that is, urea derivatives, amine hydrochlorides, and N-chloroamines were produced, simultaneously. The latters were reduced with sodium bisulfite to give amine hydrochlorides. The mechanism of these reaction was also discussed.

We have found that N,N-dibromobenzenesulfonamide, N-bromo-N-benzylbenzenesulfonamide, and bromine react with benzylamines affording lower substituted amines, *i.e.*, tertiary benzylamine degraded to secondary benzylamine hydrobromide and benzaldehyde, secondary benzylamine to primary benzylamine hydrobromide and benzaldehyde, and primary benzylamine to ammonium bromide and benzaldehyde, respectively.[3]

No stable product has been obtained on the reaction of other aliphatic amines with N-bromosulfonamides. Reaction with N-chloroamide was expected to give isolable products because of the relative mildness of its reactivity.

N-chloro- and N,N-dichlorophenylacetamides have been synthesized[4] by the modified method of Foglia[5] who has obtained N,N-dichlorourethane.

The reactions of N,N-dichlorophenylacetamide (I) with diethylamine (II), piperidine (IV), and 2-ethylpiperidine (VI) yielded urea derivatives such as III, V, and VII besides, hydrochlorides of corresponding amines, II, IV, and VI, respectively.

Reaction of N,N-dichlorophenylacetamide (I) with diethylamine in 1: 4 molar ratio in carbon tetrachloride gave the crystals of diethylamine hydrochloride under the evolution of heat. After the removal of them, evapolation of the solvent from the filtrate, showed positive KI-starch reaction, caused a vigorous decomposition of the solute leaving a black residue giving out a strong amine-like odor. To avoid this, the solute in the filtrate was reduced by shaking with a saturated aqueous sodium bisulfite. The organic layer was subjected to column chromatography on a silica gel column. Elution of the column with chloroform gave an oil (III), $C_{12}H_{18}ON_2$, bp_3 150—158°, which solidified after allowing it to stand, mp 44° (from *n*-hexane), in 40% yield. This showed absorption bands at 1630 cm^{-1} (ν_{NCON}), and 3300 cm^{-1} (ν_{NH}) in the infrared region. Signals in the nuclear magnetic resonance (NMR) spectrum indicated the presence of aromatic five protons (δ=7.25, 5H (s)), benzylic two protons (δ=4.40, 2H (s)), and ten portons of two ethyl groups (δ=3.25, 4H; δ=1.11, 6H). Catalytic reduction of III over palladium-carbon in methanol afforded N,N-diethylurea (VIII) and toluene. Reflux of III with 5% sulfuric acid for a long period gave N,N'-dibenzylurea (IX). On the basis of the above spectral and chemical evidences, III is assumed

1) Part XV: Y. Kamiya and S. Takemura, *Chem. Pharm. Bull.* (Tokyo), **20**, 2471 (1972).
2) Location: *Kowakae, Higashi-Osaka, Osaka.*
3) S. Takemura, H. Terauchi, Y. Kamiya, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **17**, 523 (1969).
4) H. Terauchi and S. Takemura, *Chem. Pharm. Bull.* (Tokyo), **20**, 1821 (1972).
5) T.A. Foglia and B. Swern, *J. Org. Chem.*, **31**, 3625 (1966).

as N,N-diethyl-N′-benzylurea. Structure of III was further confirmed by the comparison of IR spectra and mixed melting point determination with authentic sample synthesized by another route.

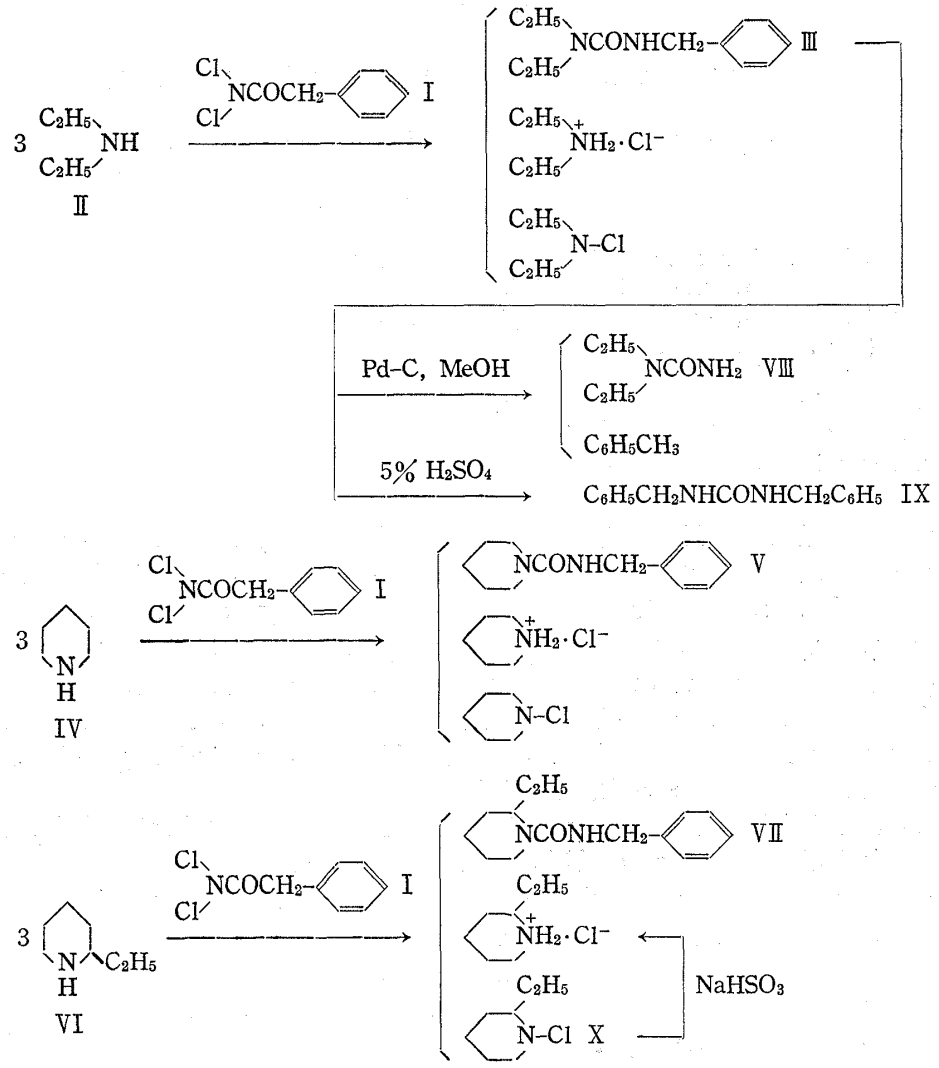

Chart 1

The treatments of piperidine (IV) and 2-ethylpiperidine (VI) with I in the similar manner gave corresponding products, respectively. N,N-Dichlorophenylacetamide (I) was allowed to react with piperidine (IV) as descrived in the reaction of I with II to obtain crystalline hydrochloride of IV in 28% yield. After the removal of the hydrochloride, the filtrate was treated in a similar manner as in the case of I with II gave colorless crystals of mp 98—100° (from C_6H_6–*n*-hexane), $C_{13}H_{18}ON_2$, in 25% yield. The IR spectrum (nujol) exhibited at 1620 cm^{-1} (ν_{NCON}), and 3300 cm^{-1} (ν_{NH}). The NMR spectrum in deuterochloroform proved the existence of ten protons on the piperidine ring (δ=1.56, 6H(m); δ=3.22, 4H(m)), the benzylic protons (δ=4.38, 2H(s)), one proton due to the -NH (δ=4.75, 1H(br)), and five protons on the benzene ring (δ=7.25, 5H(s)). These data indicate that V is an analogue of III, benzylcarbamoylpiperidine (V). 2-Ethylpiperidine (VI) was also made to react with I to give crystalline hydrochloride of VI in 40% yield. After the removal of the hydrochloride, similar treatment of the mother liquor as described above gave crystals of mp 71—73° (from *n*-hexane), VII, $C_{15}H_{22}ON_2$, in 37% yield. IR spectrum (nujol) of them exhibits at 1610 cm^{-1} (ν_{NCON}), and 3300 cm^{-1} (ν_{NH}). Signals in the NMR indicated the presence of piperidine ring (δ=1.6, 6H on C-3,4, and 5(m); δ=2.7, 1H on C-2(m); δ=3.8, 2H on C-6(m)), ethyl group

(δ=0.88, 3H(t), J=7 cps; δ=1.6, 2H(m)), and benzyl group (δ=4.41, benzylic 2H(s); δ=7.28, 5H(s), benzene ring). On these data, this compound should be given the structure of benzylcarbamoyl-2-ethylpiperidine (VII).

In these reactions, formation of labile by-products, positive for KI-starch reaction, were proved. By the treatments with aqueous sodium bisulfite, they were disappeared on thin-layer chromatograms. Additional some experiments were carried out about these KI-starch reaction positive substances; after the reaction of I with VI as described above, the mother liquor, separated from crystalline hydrochloride of VI, was immediately chromatographed. The column was eluted with carbon tetrachloride to collect a fraction of positive for KI-starch reaction (X). The solution of X was decomposed immediately after the removal of the solvent leaving a dark colored oily residue. When the solution containing X was allowed to stand at room temperature or reduced with aqueous sodium bisulfite, the hydrochloride of VI was obtained. This labile substance is, on these results, likely N-chloro-2-ethylpiperidine.

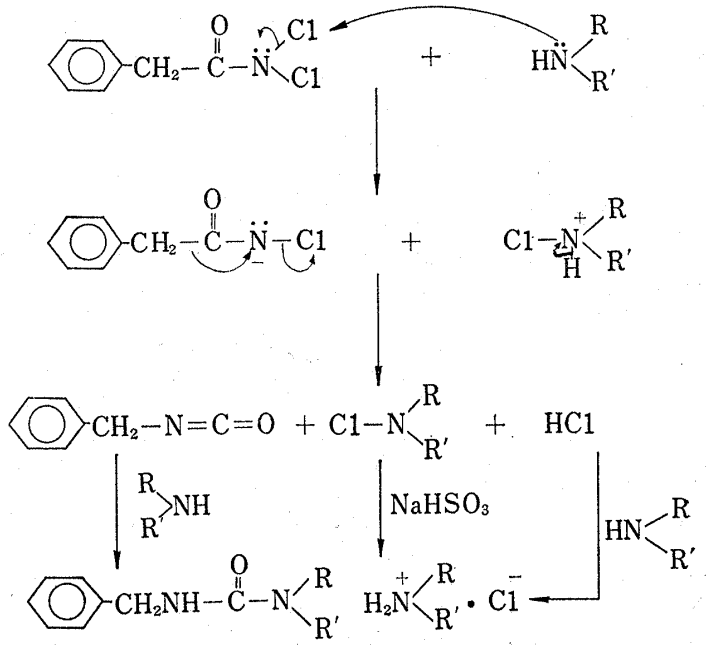

Chart 2

These reactions of I with amines may start with an attack of lone pair of the nitrogen atom of amines to one of the chlorines of I producing X, and release of the other chlorine atom of I as an anion, followed by a rearrangement of benzyl group may give benzyl isocyanate which reacts with free amines to give urea derivatives. Thus one molar I seems to react with three molar amines. Tertiary amine, such as N-ethylpiperidine gave a mixture of undesirable products which were difficult to separate each other.

Experimental

N,N-Dichlorophenylacetamide (I)[4]——Into the mixture of AcONa (28 g), AcOH (2.8 ml), H_2O (120 ml), $CHCl_3$ (100 ml), and phenylacetamide (18.4 g), Cl_2 was bubbled through for 4 hr. The yellow organic phase was washed with H_2O, dried over Na_2SO_4, and the solvent was distilled off to leave a yellow oil (34.5 g). IR $\nu_{max}^{liq.}$ cm^{-1}: 1720 (ν_{CON}).

Reaction of N,N-Dichlorophenylacetamide (I) with Diethylamine (II)——A solution of N,N-dichlorophenylacetamide (I) (5 g, 0.024 mole) in CCl_4 (20 ml) was dropwise added to the cooled (13—16°) and stirred mixture of diethylamine (II) (7.1 g, 0.097 mole) and CCl_4 (20 ml). After the addition of the solution, the stirring was continued for additional 1 hr. The separated II-HCl was filtered off, and the filtrate was washed with 5% HCl to remove the excess II, stirred with saturated aq. $NaHSO_3$ (20 ml) for 1 hr, washed with H_2O, and dried over Na_2SO_4. The CCl_4 solution was condensed by distillation and the residue was charged on a column of silica gel. Elution with $CHCl_3$ gave N,N-diethyl-N'-benzylurea (III), bp_3 150—158°, in 40% yield. Recrystallization of this from *n*-hexane gave colorless crystals of mp 44°. These were identified with an authentic sample, synthesized by other route, by mixed melting point determination and the comparison of IR spectra. *Anal.* Calcd. for $C_{12}H_{18}ON_2$: C, 69.85; H, 8.80; N, 13.59. Found: C, 70.10; H, 8.75; N, 13.50.

Reactions of N,N-Diethyl-N'-benzylurea (III)——1) III (2 g) was reduced over Pd-C in MeOH for 4 hr. The product was distilled *in vacuo*, toluene in the distillate was detected by gas chromatography by showing identical retention time with authentic sample. The residue of the distillation was chromatographed on a silica gel column to give a colorless oil, VIII, bp_3 130—140°, in 30% yield. The oil was identified with

authentic N,N-diethylurea[6] by comparison of IR. 2) III (1 g) was refluxed with 5% H_2SO_4 for 8 hr. The mixture was extracted with $CHCl_3$, the $CHCl_3$-layer was washed with H_2O, dried over Na_2SO_4, and the solvent was distilled off. The residue was recrystallized from dil. EtOH to obtain colorless needles, (IX), mp 166—168° (50 mg). These were identified with authentic sample of N,N'-dibenzylurea by mixed melting point determination and the comparison of IR.

N,N-Diethyl-N'-benzylurea (III)——A solution of $COCl_2$ (1.35 g, 0.018 mole) in toluene was mixed with diethylamine (1 g, 0.013 mole) under cooling. After the mixture was allowed to stand for 3 hr at room temperature, benzylamine (1.39 g, 0.013 mole) was added under cooling. After 2 hr, the solvent was removed under reduced pressure, and the residue was chromatographed on a column of silica gel. An oil (1 g), bp_3 150—158° (III) was obtained by elution of the column with $CHCl_3$–MeOH. It was recrystallized from *n*-hexane to obtain it in crystalline form, mp 44°. Subsequent elution of the column gave N,N'-dibenzylurea[7] (0.3 g), mp 166—168° (from EtOH–H_2O).

Reaction of I with Piperidine (IV)——A solution of I (10 g, 0.05 mole) in CCl_4 (50 ml) was added to a mixture of IV (16 g, 0.19 mole) and CCl_4 (50 ml) under cooling (13—16°) and stirring. The stirring was continued for following 1 hr. The separated crystals of IV-HCl (28%) were filtered off, the filtrate was washed with 10% HCl to remove excess IV, the organic phase was stirred with saturated aqueous $NaHSO_3$ (50 ml) for 1 hr, and washed with H_2O, and dried over Na_2SO_4. The solvent was distilled off from the solution to leave an oil which was subjected on a column of silica gel, followed by elution with $CHCl_3$. From the eluate, colorless needles, mp 98—100° (from C_6H_6–*n*-hexane) were obtained in 25% yield. IR ν_{max}^{Nujol} cm^{-1}: 3300 (ν_{NH}), 1620 (ν_{NCON}). *Anal.* Calcd. for $C_{13}H_{18}ON_2$: C, 71.51; H, 8.32; N, 12.83. Found: C, 71.10; H, 8.19; N, 12.50.

Reaction of I with 2-Ethylpiperidine (VI)——1) A solution of VI (25 g, 0.22 mole) in CCl_4 (50 ml) was mixed with a solution of I (11.3 g, 0.055 mole) in CCl_4 (50 ml) under cooling (13—16°) and continuous stirring. Crystals of VI-HCl separated after the solution was stirred for 1 hr (40% yield). They were filtered off by suction. The filtrate was treated with aq. HCl, followed with aq. $NaHSO_3$, as described above. The CCl_4 solution was then washed with H_2O, dried over Na_2SO_4 and chromatographed by elution with CCl_4. From the eluate, colorless crystals of mp 71—73° (from *n*-hexane) were obtained in 37% yeild. IR ν_{max}^{Nujol} cm^{-1}: 3300 (ν_{NH}), 1610 (ν_{NCON}). *Anal.* Calcd. for $C_{15}H_{22}ON_2$: C, 73.11; H, 9.01; N, 11.37. Found: C, 73.28; H, 8.90; N, 11.20. 2) To VI (12.5 g, 0.11 mole) in CCl_4 (20 ml), a solution of I (5.6 g, 0.028 mole) in CCl_4 (20 ml) was added under stirring at 13—16°. After continuous stirring for 1 hr, the separated crystalline VI-HCl was filtered off. The filtrate was treated with 5% HCl to remove excess of VI, washed with H_2O, and dried over N_2SO_4. The solution was condensed *in vacuo* to almost dryness (not to completely). This showed two spots at *Rf* 0.69 and 0.24 (VII) on thin-layer chromatogram. The residue was passed through a short column of silica gel to obtain a fraction which corresponds to the spot of *Rf* 0.69 (X). Evaporation of the solution even under low temperature caused a vigorous decomposition of the solute with evolution of heat and amine-like odor leaving a dark colored oil. The solution showed positive KI-starch reaction, and on allowing it at room temperature crystalline VI-HCl was obtained. Treatment of the solution with aq. $NaHSO_3$, followed by evaporation of the solvent also gave VI-HCl which was identified with authentic one by comparison of IR.

6) T.L. Davis and K.C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1798 (1929).
7) O.C. Dermer and J. King, *J. Org. Chem.*, **8**, 168 (1943).