# Heterocycles. 9. 2-Aryl-2*H*-1,4-tetrahydrooxazines (1,2)



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Reaction of 2-bromo-1-phenylethanones with diethanolamine gave 2-hydroxymorpholines. Acetylation gave mono or diacetates. Acid catalyzed dehydrations gave several types of products whose structures are discussed.

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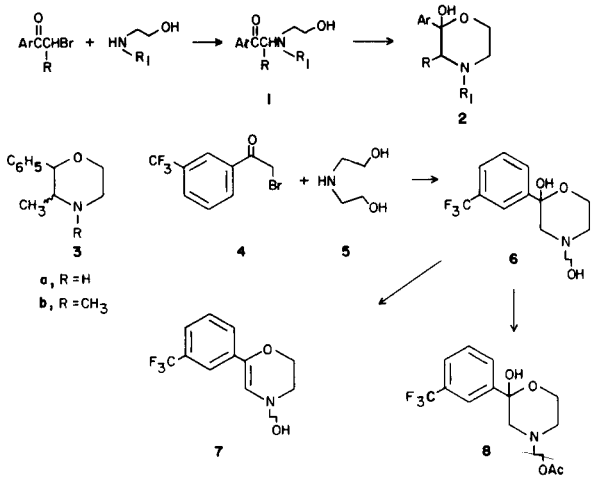
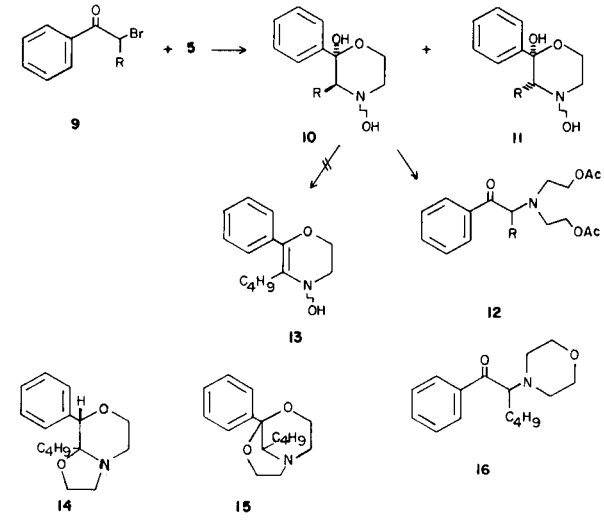
The phenacylaminoalcohols **1** formed initially in the reaction of α-phenacylbromide and *N*-alkylethanolamines, cyclize spontaneously to the hemiketal structure **2** (3). We were interested in using diethanolamine in this reaction hoping the resulting hemiketal would serve as an intermediate to some novel anorectic agents. We based our hopes by analogy to the known anorectic agents Phenmetrazine (4) (**3a**) and Phendimetrazine (4) (**3b**). We wish to report here the reaction of α-phenacylbromide with diethanolamine and some novel chemistry of several of the resulting products.

Reaction of α-bromo-3-trifluoromethylacetophenone (**4**) with diethanolamine (**5**) gave hemiketal **6**. In analogy to our previous work (1), we were able to dehydrate **6** to the



unstable dihydrooxazine **7**. Reaction of **6** with excess acetic anhydride gave a monoacetate **8** in which the hemiketal function remained intact.

Reaction of α-bromopropiophenone (**9**, R = $CH_3$) with **5** gave two hemiketals, one melting at 81-83° and the other melting at 111-112°. The former analyzed as a hydrate which on drying at 56° in vacuum lost the water of hydration and melted at 111-112°. The possibility of diastereoisomer formation during ring closure was previously studied but no separation into diasteriomeric pairs could be demonstrated (5). Examination of the proton resonances of these two compounds in deuteriochloroform



showed dramatic differences in the ratio of methyl absorptions. Thus, the lower melting compound had doublets at 0.67, 0.82 and 1.28 ppm in the ratio of 87:9:4, respectively. The other compound had a similar set of doublets in the ratio 13:74:13, respectively which in DMSO-$d_6$ was 2:91:7. The doublet at 1.28 ppm is assigned to the open chain isomer by comparison of its spectrum to the diacetate (**12**, R = $CH_3$). These compounds are undoubtedly in dynamic equilibrium in solution, but we did not investigate this point. In contrast to the above monoacetylation of **6**, treatment of **10** or **11** with acetic anhydride gave only diacetate **12**.

Reaction of α-bromohexanophenone (**9** = *n*-$C_4H_9$) with **5** gave **10** (R = *n*-$C_4H_9$) presumably as a mixture of stereoisomers. Acetylation of this material also gave diacetate **12** (R = *n*-$C_4H_9$). Acid catalyzed dehydration of **10** (R = *n*-$C_4H_9$) in refluxing benzene gave a crystalline, white solid which was not the expected dihydrooxazine **13** as deduced from its nmr and uv spectra. Elemental analyses showed this compound to be isomeric with **13**. Three possible structures (**14-16**) for this material quickly came to mind. Inspection of the nmr spectrum eliminated structure **16** as the spectrum was much too complex in the $NCH_2CH_2O$ regions. In trying to differentiate between structures **14** and **15**, one can see **14** has a benzylic methine proton which should appear as a downfield singlet. Unfortunate-

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ly, the spectrum of this compound was too complex in that region to find such a signal.

In the course of preparing more material, the reaction was run in refluxing toluene (6) and an oil obtained which was obviously not the white solid obtained previously. Nor was it the desired dihydrooxazine **10**. Inspection of its nmr spectrum revealed a downfield pair of singlets attributable to the benzylic methine proton in **14** (7). If the toluene dehydration product is **14** then the benzene dehydration product is **15**.

None of these compounds showed significant biological activity in our anorectic, cardiovascular and central nervous system screens.

## EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (potassium bromide/or neat film) were recorded on a Perkin-Elmer 521 grating spectrophotometer. Ultraviolet spectra (ethanol) were recorded on a Perkin-Elmer 350 spectrophotometer (extinction coefficients are expressed as log values). Proton magnetic resonance spectra (deuteriochloroform with internal tetramethylsilane) were run on a Varian A-60A. The standard drying agent was magnesium sulfate and solvents were removed *in vacuo* on a rotary evaporator. Kieselgel was used for chromatography.

Tetrahydro-2-hydroxy-4-(2-hydroxyethyl)-2-[3-(trifluoromethyl)phenyl]-2*H*-1,2-oxazine (**6**).

A stirred solution of 3-trifluoromethylacetophenone (51.6 g., 0.274 mole) in chloroform (650 ml.) was treated dropwise with a solution of bromine (45.0 g., 0.281 mole) in chloroform (150 ml.). After the addition was completed, the solvent was removed to give bromoketone **4**.

The bromoketone **4** was added slowly to diethanolamine **5**, (57.6 g., 0.549 mole) using a water bath to keep the temperature below 30°. After 0.5 hour, the reaction mixture was diluted with water and the resulting precipitate was filtered off, washed with water and dried. The solid was crystallized from aqueous methanol to give **8** (19.4 g., 24.3%), m.p. 110-117°. An analytically pure sample was prepared by stirring the above solid with diethylether and filtering the solid, m.p. 116.5-119°; ir: $\nu$ 3400, 1455, 1435, 1335, 1230, 1115 $cm^{-1}$; uv: $\lambda$ 250 (2.538), 256 (2.619), 262 (2.697), 269 (2.608); nmr (DMSO-$d_6$): $\delta$ 2.05-2.63 (4.5H, m), 2.86 (2H, d, J = 11 Hz), 3.33-3.88 (3H, m), 4.02 (1H, d of d, J = 3 Hz, 16 Hz), 4.25-4.63 (1H, m, exchangeable), 6.57 (0.8H, s, exchangeable), 7.57-8.07 (4H, m).

*Anal.* Calcd. for $C_{13}H_{16}F_3NO_3$: C, 53.61; H, 5.54; N, 4.81. Found: C, 53.79; H, 5.56; N, 4.62.

The maleate of **6** was prepared by adding maleic acid (0.86 g., 7.4 mmoles) in diethyl ether to a solution of **8** (2.05 g., 7.45 mmoles) in the same solvent. A viscous liquid separated and solidified on standing. The solid was crystallized from ethyl acetate to give **6** maleate (2.16 g., 74.2%), m.p. 117-120°; ir: $\nu$ 3450-2400, 1695, 1610, 1580 $cm^{-1}$; uv: $\nu$ 256 sh (3.002), 263 (2.964), 269 (2.851); nmr (DMSO-$d_6$): $\delta$ 2.92-3.53 (6H, m), 3.63-3.97 (2.7H, m), 4.00-4.51 (2H, m), 6.13 (2H, s), 7.32-8.10 (5H, m).

*Anal.* Calcd. for $C_{17}H_{20}F_3O_7$: C, 50.13; H, 4.95; N, 3.44. Found: C, 50.03; H, 4.90; N, 3.36.

Dihydro-4-(2-hydroxyethyl)-2-[3-(trifluoromethyl)phenyl]-2*H*-1,4-oxazine (**7**).

A stirred mixture of **6** (19.5 g., 67.0 mmoles), *p*-toluenesulfonic acid (0.58 g.) and toluene (400 ml.) under positive nitrogen atmosphere was heated to reflux under a Dean-Stark water separator for 18 hours. The cooled mixture was treated with solid potassium carbonate, and washed with saturated aqueous sodium bicarbonate, treated with charcoal, filtered and concentrated to a dark brown liquid. This was purified by chromatography (on 500 g.) eluting with benzene-acetone-triethylamine (93:5:2) give **7** (7.18 g., 39.2%) as a yellow-brown liquid, b.p. 160-165/0.1 mm (Kugelrohr); ir: $\nu$ 3380, 1645, 1605, 1585 $cm^{-1}$; uv: $\lambda$ 240 (3.679), 329 (4.087); nmr (DMSO-$d_6$): $\delta$ 3.27 + 3.41 (4H, pr overlapping t, J = 5 Hz and 4 Hz) 3.72 (2H, br, s, changing to t on deuterium oxide exchange), 4.28 (2H, t, J = 4 Hz), 4.83 (1H, br, s, exchangeable) 6.83 (1H, s), 7.22-7.88 (4H, m).

*Anal.* Calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 56.88; H, 5.15; N, 5.04.

4-(2-Acetoxyethyl)tetrahydro-2-hydroxy-2-[3-(trifluoromethyl)phenyl-2*H*-1,4-oxazine (**8**).

Alcohol **6** (30 g. of crude material) was treated with acetic anhydride (20 ml.) and pyridine (35 ml.) at room temperature for 18 hours. The mixture was poured into water and extracted with diethylether (twice). The combined organic layer was washed with saturated aqueous sodium bicarbonate, dried, treated with charcoal, filtered and concentrated. The residue was chromatographed (on 1.5 kg.) eluting with benzene-acetone-triethylamine (96.5:2.5:1) (4 l.) and benzene-acetone-triethylamine (94:5:1) and taking 1 l. fractions. Fractions 11-13 were combined and concentrated to give **8** as a yellow liquid (13.9 g., 35.9%), ir: $\nu$ 3450, 1735, 1330, 1230, 1160, 1120, 1070 $cm^{-1}$; uv: $\lambda$ 256 (2.766), 269 (2.690), 332-343 (1.644); nmr: $\delta$ 2.07 (3H, s), 2.20-3.03 (6H, m), 3.65-4.47 (4H, m), 4.70 (1H, s, exchangeable), 7.32-8.03 (4H, m).

*Anal.* Calcd. for $C_{15}H_{18}F_3NO_4$: C, 54.05; H, 5.44; N, 4.20. Found: C, 54.24; H, 5.48; N, 4.00.

Tetrahydro-2-hydroxy-4-(2-hydroxyethyl)-3-methyl-2-phenyl-2*H*-1,4-oxazine (**10** and **11**, R = $CH_3$).

To a solution of diethanolamine (**5**, 22 g., 0.21 mole) in water (20 ml.) at 5° was added dropwise $\alpha$-bromopropiophenone (**9**, R = $CH_3$, 21.3 g., 0.10 mole). Dioxane (100 ml.) was added and the solution was heated at 45° for 1 hour and cooled to 5° for 3 hour. The solution was diluted with 10% aqueous sodium hydroxide and extracted with diethylether (3 times). The ether was dried and the product isolated by precipitating with an ethereal solution of maleic acid. The solid was filtered off and crystallized twice from ethyl acetate to give a white solid **6**, (12 g., 34%), m.p. 131-132°.

*Anal.* Calcd. for $C_{13}H_{19}NO_3 \cdot C_4H_4O_4$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.86; H, 6.67; N, 3.88.

A stirred solution of $\alpha$-bromopropiophenone (184.1 g., 0.864 mole) in 2-propanol (600 ml.) was treated with **5** (234 g., 2.22 moles) and stirred overnight at room temperature. The solvent was concentrated and the residue partitioned between diethylether and saturated sodium bicarbonate. The aqueous phase was washed with diethylether. The combined ether layers (1.4 l.) was backwashed with water. On standing in the separatory funnel, crystals came out. These were filtered off to give a white solid A (11.3 g., 5.5%). The ether layer was dried, treated with charcoal, filtered and concentrated to *ca.* 500 ml. The resulting crystals were filtered off, washed with diethylether 50% hexane (300 ml.), hexane (200 ml.) and dried to give a white solid B (57.0 g., 27.8%), m.p. softens at 80°, melts by 110°. The combined filtrate and wash were concentrated to *ca.* 500 ml. The crystals were filtered off, washed as above and dried to give a pale yellow solid C (109.1 g., 53.3%), m.p. 106-108°.

The sample of C (9.89 g.) was recrystallized from hot toluene (100 ml.) to give a first crop of white solid (3.0 g.), m.p. 81-83°. A second crop of white solid (5.92 g.), m.p. 112-113.5°, was obtained from the combined filtrate and wash (hexane).

Low Melting Isomer.

This compound had ir: $\nu$ 3580, 1680 (vw) 1450, 1140, 1080, 1060, 700 $cm^{-1}$; uv: $\lambda$ 226 sh (2.410), 230 (2.551), 236 (2.544), 242 (2.486), 248 (2.312), 252 (2.076), 271 (1.519); nmr: $\delta$ 0.67 + 0.82 + 1.28 (3H, trio of d, J's = 7 Hz, 6 Hz and 7 Hz, respectively, ratio of peaks 43/4.5/2), 2.08-3.17 (5H, m), 3.35-4.53 (6H, m, contains 2 exchangeable protons), 7.08-7.75 (5H, m).

*Anal.* Calcd. for $C_{13}H_{19}NO_3 \cdot H_2O$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.44; H, 8.04; N, 5.51.

After drying at 56° under high vacuum.

*Anal.* Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.65; H, 8.07; N, 5.87.

High Melting Isomer.

This compound had ir: $\nu$ 3360, 1445, 1070, 980, 700 $cm^{-1}$; uv: $\lambda$ 224 (2.920), 250 sh (2.885), 257 sh (2.756), 263 sh (2.531), 267 sh (2.318), 280 (2.004); nmr: $\delta$ 0.69 + 0.85 + 1.29 (3H, trio of d, J's = 7 Hz, 6.5 Hz, and 7 Hz, respectively, ratio of peaks 1/5.7/1), 2.03-3.23 (5H, m), 3.40-4.58 (6H, m, diminishes by 1H on addition of deuterium oxide), 3.86-4.45 + 4.58-4.83 (5H, pr of m); (DMSO-$d_6$): $\delta$ 0.58 (trace, d, J = 7 Hz), 0.75 (2.7H, d, J = 6.5 Hz), 1.17 (0.3H, d, J = 7 Hz), 2.04-3.10 (6H, m), 3.91 + 4.09 (1H, pair of of d, J's = 3.5 Hz), 4.17-4.58 (1H, m), 6.03 (1H, s), 7.12-7.70 (5H, m).

*Anal.* Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.78; H, 8.13; N, 5.77.

Tetrahydro-3-butyl-2-hydroxy-4-(2-hydroxyethyl)-2-phenyl-2*H*-1,4-oxazine (**10/11**) (R = $C_4H_9$).

A mixture of **5** (57.4 g., 0.546 mole) and $\alpha$-bromohexanophenone (69.6 g., 0.273 mole) in benzene (500 ml.) was stirred four days at 23°. The reaction mixture was poured into saturated sodium bicarbonate, the organic layer separated, washed with saturated bicarbonate, dried, treated with charcoal, filtered and concentrated to a yellow liquid. This was purified by chromatographying twice (eluting with ethyl acetate) to give 39.4 g. of a light yellow oil which was crystallized from diethylether-hexane to a white solid (33.8 g., 44.9%), m.p. 74-75°; ir: $\nu$ 3400, 1680 (w), 1445, 700 $cm^{-1}$; uv: $\lambda$ 244 (3.439), 282 (2.587); nmr: $\delta$ 1.35-1.58 (9H, m), 2.25-2.97 (5H, m), 3.35-4.47 (6H, m), 7.25-8.13 (5H, m).

*Anal.* Calcd. for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.72; H, 9.04; N, 4.79.

2-[Bis(2-hydroxyethyl)amino]-1-phenyl-1-propanone Diacetate (**12**) (R = $CH_3$).

A solution of **10/11** (R = $CH_3$) (11.3 g., 47.6 mmoles) in acetic anhydride (11 ml.) and pyridine (17 ml.) was allowed to stand overnight at room temperature. Water (100 ml.) was added and the mixture stirred 2 hours, then diluted with diethylether (100 ml.), made basic by addition of potassium carbonate. The aqueous layer was separated and extracted with ether (2 × 100 ml.). The combined organic layer and extracts was back-washed with water, dried over potassium carbonate-magnesium sulfate, treated with charcoal, filtered and concentrated. The resulting liquid was purified by chromatography eluting with toluene-acetone-triethylamine (94:5:1) to give **12** (R = $CH_3$) as a liquid (8.30 g., 54.2%); ir: $\nu$ 1730, 1040, 695 $cm^{-1}$; uv: $\lambda$ 243 (3.978), 280 (3.180); nmr: $\delta$ 1.28 (3H, d, J = 7 Hz), 1.90 (6H, s), 2.90 (4H, t, J = 6 Hz), 4.08 (4H, t, J = 6 Hz), 4.48 (1H, q, J = 7 Hz), 7.32-7.62 (3H, m), 7.96-8.17 (2H, m).

*Anal.* Calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.09; H, 7.18; N, 4.15.

2-[Bis(2-hydroxyethyl)amino]-1-phenyl-1-hexanone Diacetate (**12**) (R = $C_4H_9$).

A solution of **10/11** (10.1 g., 36.0 mmoles) was acetylated as above to give **12** (R = $C_4H_9$) (9.7 g., 83.9%), b.p. 187-193/0.025 mm (Kugelrohr); ir: $\nu$ 1735, 1680, 1230, 1040 $cm^{-1}$; uv: $\lambda$ 244 (4.034); 280 (3.220); nmr: $\delta$ 0.90 (3H, t), 1.15-1.80 (6H, m), 1.92 (6H, s), 2.89 (4H, t, J = 6 Hz), 4.08 + 4.27 (5H, t, + q, J's = 6 Hz), 7.33-7.63 (3H, m), 7.88-8.13 (2H, m).

*Anal.* Calcd. for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.90; H, 7.97; N, 3.85.

9-Butyl-5-phenyl-4,6-dioxa-1-azabicyclo[3.3.1]nonane (**15**).

A stirred mixture of **10/11** (R = $C_4H_9$) 3.4 g., 12.2 mmoles), *p*-toluenesulfonic acid hydrate (2.61 g., 13.7 mmoles) in benzene (100 ml.) was heated 5 hours at reflux under a Dean-Stark water separator. The cooled solution was extracted with saturated sodium bicarbonate, dried, treated with charocoal, filtered and concentrated to a yellow liquid which was purified by chromatography eluting with ethyl acetate to give **15** (0.98 g., 30.8%), m.p. 59-60° (aqueous methanol); ir (chloroform): 1445, 1095, 735 $cm^{-1}$; uv: $\lambda$ 225 (3.555), 258 (2.846), 264 (2.548); nmr: $\delta$ 0.55-1.90 (9H, m), 2.40-4.83 (9H, m); 7.20-7.68 (5H, m), has no exchangeable protons.

*Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.64; H, 8.82; N, 5.19.

8a-Butylhexahydro-8-phenyloxazolo[2,3-*c*][1,4]oxazine (**14**).

A stirred mixture of **10/11** (25.2 g., 90.2 mmoles), *p*-toluenesulfonic acid hydrate (18.9 g., 99 mmoles) and toluene (500 ml.) was heated 18 hours at reflux under a Dean-Stark water separator. The mixture was worked up as above to give after chromatography (twice) eluting with ethyl acetate and with ethyl acetate-hexane (60:40), 5.7 g. (24.2%) of **15** b.p. 175-182/0.1 mm (Kugelrohr); ir: $\nu$ 1095, 1070, 695 $cm^{-1}$; uv: $\lambda$ 226 (3.728), 303 (2.991); nmr: $\delta$ 0.60-2.33 (9H, m), 2.68-4.22 (8H, m), 4.50 + 4.68 (1H, pair of s in ratio of 4.7/1), 7.16-7.67 (4.8H, m), 7.94-8.18 (0.2H, m).

*Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.02; H, 8.77; N, 5.19.

## REFERENCES AND NOTES

(1) For Part **8** see P. M. Weintraub, D. R. Meyer and C. E. Aimen, *J. Org. Chem.*, **45**, 4989 (1980).

(2) Presented in part at the 11th Central Regional ACS Meeting, March, 1979.

(3) N. H. Cromwell and K. C. Tsou, *J. Am. Chem. Soc.*, **71**, 993 (1949); R. E. Lutz and R. H. Jordan, *ibid.*, **71**, 996 (1949).

(4) USAN and USP Dictionary of Drug Names, U. S. Pharmacopeial Convention, Inc., Rockville, Maryland, 1975 editon, p. 212.

(5) A. H. Beckett, W. H. Hunter and P. Kourounakis, *J. Pharm. Pharmacol.*, **20**, suppl. 2185 (1968).

(6) For this piece of serendipity we are greatly indebted to O.S.H.A.

(7) A pair of singlets is not surprising as the starting material is probably a mixture of **10** and **11**.