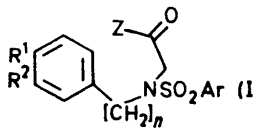
Synthesis of 1-Oxo- and 1-Hydroxy-azabenzocycloalkanes [1]

By **James Schlademan** and **Richard Partch,*** Clarkson College of Technology, Potsdam, New York 13676

The intramolecular Friedel–Crafts cyclization of various substituted glycines has been studied. The experimental conditions providing 3-arylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-one have been verified and used to synthesize similar heterocycles.

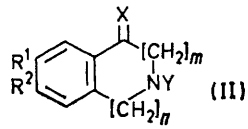
REHMAN and PROCTOR, following earlier work by von Braun,[2] have reported a route [3,4] to 3-arylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-one (IIc). Our interest in preparing benzazepinols had led us to investigate the Proctor procedure [3] before a modification [4] was published. Starting from *N*-phenethylbenzenesulphonamide, the glycyl chloride (Ib) was prepared in



(I)

a; $n = 1$, Z = Cl, $R^1 = R^2 = H$
b; $n = 2$, Z = Cl, $R^1 = R^2 = H$
c; $n = 2$, Z = OH, $R^1 = R^2 = H$
d; $n = 3$, Z = Cl, $R^1 = R^2 = H$
e; $n = 0$, Z = Cl, $R^1 = R^2 = H$
f; $n = 2$, Z = Cl, R^1 = OMe, $R^2 = H$
g; $n = 4$, Z = Cl, $R^1 = R^2 = H$

81% yield overall. When treated with 1·5 mol. equiv. of aluminium chloride in methylene chloride at −70° the acid chloride gave a high yield of 1,2,3,4-tetrahydro-*N*-phenylsulphonylisoquinoline (IIb) instead of the expected benzazepinone (IIc). This led us to study the reaction in greater detail.[5]



(II)

a; $m = 1$, $n = 1$, X = O, Y = SO_2Ar, $R^1 = R^2 = H$
b; $m = 0$, $n = 2$, X = H_2, Y = SO_2Ar, $R^1 = R^2 = H$
c; $m = 1$, $n = 2$, X = O, Y = SO_2Ar, $R^1 = R^2 = H$
d; $m = 1$, $n = 3$, X = O, Y = SO_2Ar, $R^1 = R^2 = H$
e; $m = 1$, $n = 2$, X = H,OH, Y = SO_2Ar, $R^1 = R^2 = H$
f; $m = 1$, $n = 2$, X = H,OH, Y = H, $R^1 = R^2 = H$
g; $m = 1$, $n = 2$, X = H,OH, Y = Me, $R^1 = R^2 = H$
h; $m = 1$, $n = 3$, X = H,OH, Y = H, $R^1 = R^2 = H$
i; $m = 0$, $n = 2$, X = H_2, Y = SO_2Ar, R^1 = Me, $R^2 = H$

An investigation of the effect of temperature on decarbonylation showed that after more than 3 h at −70° no reaction had occurred between the chloride (Ib) and 1·5 mol. equiv. of aluminium chloride. No reaction occurred at −20°. At 0° gas was evolved and the isoquinoline (IIb) was the only product.

Alkyl radicals produced in a medium of alkane, carbon tetrachloride, and peroxide have been efficiently trapped by carbon monoxide at high pressure to yield an acyl chloride.[6] We thought that the loss of carbon monoxide from compound (Ib) might be an equilibrium process which could be controlled by running the reaction in the presence of carbon monoxide under pressure. Since no decarbonylation occurred below 0° the glycyl chloride (Ib) in methylene chloride was cooled to −10°, 1·5 equiv. of aluminium chloride were added, carbon monoxide was introduced, and the mixture was allowed to warm to room temperature slowly with stirring. Experiments were performed at carbon monoxide pressures of 50 and 700 atm. The yield of the desired benzazepinone (IIc) was no greater (<5%) than in the absence of carbon monoxide.

Catalysts other than aluminium chloride, such as polyphosphoric acid [acting on the glycine acid (Ic)] and boron trifluoride–ether [acting on (Ib)], all gave the isoquinoline (IIb).

Using the excess of catalyst prescription of ref. 4 we then resumed our work on the effect of ring size variation on the cyclization. The Table shows the results.

Friedel–Crafts cyclization of substituted glycines *

Substrate	*T*/°C	Product	Yield (%)
(Ia)	−10	(IIa)	94
(Ib)	−10	(IIc)	86
(Ib)	0	(IIb)	83
(Id)	−10		*a*
(Id)	15	(IId)	36
(Ie)	−10		*b*
(If)	−10	(IIi)	*c*
(If)	25	(IIi)	86
(Ig)	0		*d*
(Ig)	25		*d*

* Aluminium chloride–substrate 3 : 1; reaction time 3—6 h.

[a] No reaction occurred. [b] Normal work-up gave tars or solids which defied crystallization and left an ash when burned. [c] No yield calculated; the product was identical with that obtained in the reaction at 25 °C. [d] The major product contained no carbonyl group and was not further investigated.

The optimum temperature for the preparation of the seven-membered ring compound (IIc) is −10°. At higher temperatures the yield is decreased and an amorphous orange material is produced which greatly hinders isolation of the azepine (IIc). Formation of the eight-membered ring compound (IId) does not occur below 0°. The formation of the isoquinolone (IIa) is especially interesting because *N*-benzylsulphonamides can be cleaved by the action of aluminium chloride.[7]

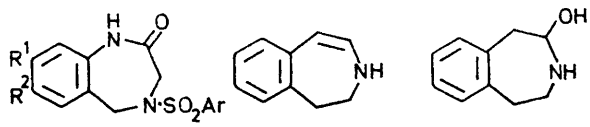
The ketones (IIa, c, and d) form 2,4-dinitrophenylhydrazones and are reduced by sodium borohydride. The isoquinolone (IIa) gives a good yield of the 1,4-benzodiazepine (III) when treated with hydrazoic acid.

We then attempted to remove the arylsulphonyl group from the benzazepinone (IIc). Refluxing hydrochloric acid and dioxan produced no reaction. Warming with

Presented at the 160th A.C.S. Meeting, Chicago, September 1970.

[2] J. von Braun, G. Blessing, and R. S. Cahn, *Ber.*, 1924, **57**, 908; J. von Braun and O. Bayer, *Ber.*, 1927, **60**, 1257.
[3] M. Rehman and G. Proctor, *J. Chem. Soc.* (*C*), 1967, 58.
[4] M. Rehman and G. Proctor, *J. Chem. Soc.* (*C*), 1969, 1321.
[5] *Cf.* M. Harmon, *Ann. Chim.* (*France*), 1965, **10**, 213; K. Likforman, J. Gardent, and M. Janot, *Compt. rend.*, 1969, **268**, 2340; E. Rothstein and W. Schofield, *J. Chem. Soc.*, 1965, 4566; V. Maksimov, *Tetrahedron*, 1965, **21**, 687.
[6] C. Theobald, U.S.P. 2,378,048 (*Chem. Abs.*, 1945, **39**, 4085); W. Thaler, *J. Amer. Chem. Soc.*, 1966, **88**, 4278.
[7] G. Proctor and R. Thomson, *J. Chem. Soc.*, 1957, 2302.

80% sulphuric acid or with 48% hydrobromic acid in the presence of phenol [8] gave a dark tar. Treatment with sodium in liquid ammonia gave a black oil, but it was found that if the ketone (IIc) was first reduced to



(III) (IV) (V)

the alcohol (IIe) subsequent metal–ammonia reduction gave 2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (IIf) in 35% yield. Finally, treatment of the ketone (IIc) with excess of lithium aluminium hydride in refluxing tetrahydrofuran for 1 week resulted in a 75% yield of the azepine (IIf). Methylation of compound (IIf) with formic acid and formaldehyde gave the alcohol (IIg).

The dihydrobenzazepine (IV) is reported to undergo ready hydration to give either alcohol (IIf) or (V).[9] Since (V) is an α-amino-alcohol, and these are usually unstable, the product is probably (IIf). The m.p. reported is the same as that of our compound.

EXPERIMENTAL

M.p.s are corrected. Dry methylene chloride refers to the commercial reagent stored over anhydrous magnesium sulphate. Standard procedures were used to prepare all *N*-arylbenzenesulphonamides and *N*-aralkyl-*N*-phenylsulphonylglycines.[10]

1,2,3,4-*Tetrahydro*-N-*phenylsulphonylisoquinoline* (IIb).—*N*-Phenethyl-*N*-phenylsulphonylglycine (15·1 g, 0·047 mol) and thionyl chloride (8 g) in benzene (75 ml) were refluxed for 2 h. The benzene and excess of thionyl chloride were removed under reduced pressure, leaving the glycyl chloride (Ib) as a viscous brown liquid. This was dissolved in methylene chloride (55 ml) and the solution was added slowly (2 h) to a vigorously stirred suspension of anhydrous aluminium chloride (9·4 g, 0·071 mol) in methylene chloride (110 ml) kept at −70°. Stirring was continued and the mixture was allowed to reach room temperature overnight. This mixture was then shaken with ice–water (200 ml), N-sodium hydroxide, and water, dried ($MgSO_4$), and evaporated to give compound (IIb) (13·3 g) as needles, m.p. 155—156° [from benzene–hexane (1 : 1)] (lit.,[2] 154°).

Effect of Temperature on Formation of Isoquinoline (IIb).—After the addition of the glycyl chloride solution (as above) was complete (3·75 h) the temperature was maintained at −70° for 0·5 h. Then, a sample (50 ml) of the mixture was withdrawn and quenched in ice–water (150 ml). The temperature was allowed to rise to −20° and a second 50 ml portion was withdrawn and quenched. Work-up of the two portions gave the starting glycyl chloride as a brown gum which was reconverted into the acid by gentle refluxing with 2N-sodium hydroxide followed by acidification with 6N-hydrochloric acid. The rest of the mixture gave only the isoquinoline (IIb).

Effect of Carbon Monoxide on Formation of the Isoquinoline (IIb).—*General procedure.* The glycyl chloride (Ib) (8·0 g) was dissolved in methylene chloride (100 ml) and poured into a pressure vessel which had been cooled to −20°. To this was added anhydrous aluminium chloride (3·75 g, 0·0282 mol). The vessel was then pressurized with carbon monoxide and stirred for at least 4·5 h until room temperature had been reached. The mixture was then shaken with crushed ice and dilute hydrochloric acid. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Reaction at 50 atm. A beige solid (5·8 g) was obtained; this (3·50 g) was chromatographed on neutral alumina. Elution with benzene gave isoquinoline (IIb) (1·81 g). Elution with benzene–methanol (1 : 1) gave a yellow solid (1·25 g). This was rechromatographed and crystallized (MeOH) to give the benzazepinone (IIc) (250 mg), m.p. 143—144° (Found: C, 64·1; H, 5·15; N, 4·7. Calc. for $C_{16}H_{15}NO_3S$: C, 63·8; H, 5·0; N, 4·65%).

Reaction without carbon monoxide. The reaction was carried out in the same vessel used in the reaction at 50 atm and gave the same results. A trace of the benzazepinone (IIc) was isolated.

Reaction at 700 atm. This gave a mixture of isoquinoline (IIb) and the starting glycyl chloride.

Reaction of N-Phenethyl-N-phenylsulphonylglycine with Polyphosphoric Acid.—The acid (Ic) (5·0 g) in polyphosphoric acid (65 g) was heated to 100°. After 45 min the mixture was filtered, made alkaline with 10N-sodium hydroxide, and extracted with ether. The extract was dried ($MgSO_4$) and the ether was removed by flash distillation to give a light brown liquid (1 ml) which was treated with benzenesulphonyl chloride in 2N-sodium hydroxide to give the isoquinoline (IIb).

Reaction of the Glycyl Chloride (Ib) *with Boron Fluoride–Ether.*—The acid chloride (8·3 g) and boron fluoride–ether (7·8 g) in methylene chloride (150 ml) were refluxed for 24 h and set aside at room temperature for an additional 36 h. The mixture was poured on ice and the methylene chloride layer washed with N-sodium hydroxide and water and dried ($MgSO_4$). Solvent removal gave only the isoquinoline (IIb).

2,3,4,5-*Tetrahydro*-3-*phenylsulphonyl*-1H-3-*benzazepin*-1-*one* (IIc).—*Low temperature reaction.* The glycyl chloride (Ib) [from (Ic) (12·0 g) and thionyl chloride (25 ml)] was dissolved in methylene chloride (300 ml) and cooled to −70°. To this was added anhydrous aluminium chloride (15·0 g, 0·113 mol) with vigorous stirring. The stirring was continued and the solid carbon dioxide–acetone bath was replaced with an ethanol–ice bath. The temperature was allowed to rise to −10° over 3·5 h and the reaction was quenched by shaking with a mixture of crushed ice (300 ml) and concentrated hydrochloric acid (30 ml). The organic layer was washed with dilute hydrochloric acid, water, and saturated brine, and dried ($MgSO_4$). Removal of the methylene chloride under reduced pressure and crystallization (EtOH) of the resulting solid gave the benzazepinone (IIc) (9·4 g, 86%), m.p. 145—147°, τ ($CDCl_3$) 7·0 (2H, t), 6·3 (2H, t), 5·8 (2H, s), and 3·0—2·5 (9H, m).

Reaction at 0 °C. The above reaction was repeated at 0°. Crystallization (EtOH) gave benzazepinone (IIc) (78%).

Room temperature reaction. The above reaction was repeated without cooling and gave an orange-brown solid. Crystallization (EtOH) gave benzazepinone (IIc) (44%).

Attempted Preparation of 1-Phenylsulphonylindolin-3-one.—The acid chloride (Ie) [from acid (11 g)] was dissolved in

[8] H. Snyder and R. Heckert, *J. Amer. Chem. Soc.*, 1952, **74**, 2006, 4864.

[9] J. Gardent and G. Hazebroucq, *Bull. Soc. chim. France*, 1968, 600.

[10] See examples in refs. 2, 3, and 7.

methylene chloride (300 ml) and cooled to −60°. Aluminium chloride (15 g, 0·113 mol) was added with vigorous stirring. Stirring was continued, the temperature was allowed to rise to −10° over 5 h, and the reaction was then quenched by shaking with a mixture of crushed ice (300 ml) and concentrated hydrochloric acid (30 ml). The dried ($MgSO_4$) methylene chloride layer was evaporated to give a brown intractable tar which left an ash when burned.

1,2,3,4-*Tetrahydro*-2-*phenylsulphonylisoquinol*-4-*one* (IIa).—The glycyl chloride (Ia) [from acid (11 g)] was dissolved in methylene chloride (300 ml) and the solution cooled to −60°. To this was added anhydrous aluminium chloride (15 g, 0·113 mol) with vigorous stirring. The temperature was allowed to rise to −11° over 4 h and the reaction was quenched by shaking with concentrated hydrochloric acid (30 ml) in crushed ice (300 ml). The methylene chloride layer was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting solid was crystallized (EtOH) to give the *isoquinoline* (IIa) (9·7 g, 94%), m.p. 149—150° (Found: C, 63·5; H, 4·6. $C_{15}H_{13}NO_3S$ requires C, 62·7; H, 4·55%), τ ($CDCl_3$) 5·8 (2H, s), 5·3 (2H, s), and 2·7—1·7 (9H, m).

1,2,3,4-*Tetrahydro*-7-*methoxy*-2-*phenylsulphonylisoquinoline* (IIi).—*Room temperature reaction.* The glycyl chloride (If) [from acid (10 g)] was dissolved in methylene chloride (300 ml) and aluminium chloride (15 g, 0·113 mol) was added with vigorous stirring. After 2 h the reaction was quenched by shaking with concentrated hydrochloric acid (30 ml) in crushed ice (250 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting solid crystallized (EtOH) to give the *isoquinoline* (IIi) (7·4 g, 86%), m.p. 135—137° (Found: C, 63·35; H, 5·65. $C_{16}H_{17}NO_3S$ requires C, 63·3; H, 5·55%).

Low temperature reaction. The reaction was repeated with cooling of the solution to −50° before addition of the aluminium chloride. The temperature was allowed to rise to −10° over 5 h. Work-up as before gave only the isoquinoline (IIi).

3,4,5,6-*Tetrahydro*-4-*phenylsulphonyl*-3-*benzazocin*-2(1H)-*one* (IId).—The glycyl chloride (Id) [from acid (9·3 g)] was dissolved in methylene chloride (700 ml), cooled to −10°, and mixed with aluminium chloride (15 g, 0·113 mol) with vigorous stirring. The mixture was allowed to reach room temperature over 9 h, then shaken with concentrated hydrochloric acid (40 ml) and crushed ice (700 ml). Evaporation of the dried ($MgSO_4$) methylene chloride layer left a brown viscous oil which slowly solidified. This was chromatographed on a dry column of silica gel, with chloroform as eluant; the progress of the components was followed by u.v. illumination. The highly fluorescent initial fractions were discarded. The less fluorescent, colourless, middle fractions were combined and evaporated under reduced pressure. The cream solid obtained was crystallized (MeOH) to give the *benzazocinone* (IId) (3·15 g, 36%), m.p. 119—121° (Found: C, 65·2; H, 5·5. $C_{17}H_{17}NO_3S$ requires C, 64·75; H, 5·45%), τ ($CDCl_3$) 7·9 (2H, quint), 7·0 (2H, t), 6·2 (2H, t), 5·4 (2H, s), and 2·3—1·6 (9H, m).

Attempted Cyclization of the Glycyl Chloride (Ig).—Acid chloride (Ig) and aluminium chloride (1 : 3) were mixed in methylene chloride (300 ml) and maintained at either 0 or 25° for several h. Work-up as before gave a black resinous product which could not be purified by crystallization or chromatography.

4,5-*Dihydro*-4-*phenylsulphonyl*-1H-1,4-*benzodiazepin*-2(3H)-*one* (III).—To the isoquinolone (IIa) (1·0 g, 0·0035 mol) in chloroform (7 ml) was added 2·5M-hydrogen azide (2·0 ml) in chloroform. To this solution concentrated sulphuric acid (2 ml) was added dropwise with vigorous stirring. After 30 min the mixture was neutralized with saturated sodium hydrogen carbonate solution. Evaporation of the dried ($MgSO_4$) chloroform layer under reduced pressure and crystallization (EtOH) of the resulting solid gave the *benzodiazepine* (III) (0·97 g, 91%), m.p. 191—192° (Found: C, 59·65; H, 4·85; N, 9·25. $C_{15}H_{14}N_2O_3S$ requires C, 59·6; H, 4·65; N, 9·25%).

2,3,4,5-*Tetrahydro*-3-*phenylsulphonyl*-1H-3-*benzazepin*-1-*ol* (IIe).—To a hot ethanolic solution (150 ml) of compound (IIc) (6·0 g, 0·020 mol) was added sodium borohydride (0·5 g, 0·013 mol) and 1 pellet of sodium hydroxide in water (15 ml). This mixture was gently refluxed for 10 min and then diluted with water and crushed ice until a precipitate formed. Recrystallization (MeOH–H_2O) gave the *benzazepinol* (IIe) (4·66 g, 77%) (Found: C, 63·4; H, 5·6. $C_{16}H_{17}NO_3S$ requires C, 63·35; H, 5·65%).

2,3,4,5-*Tetrahydro*-1H-3-*benzazepin*-1-*ol* (IIf).—A stirred mixture of lithium aluminium hydride (4·0 g, 0·106 mol) in tetrahydrofuran (300 ml) was slowly added to compound (IIc) (12 g, 0·040 mol) in tetrahydrofuran (200 ml). Stirring was continued and the mixture was refluxed for 8 days. After cooling, water (25 ml) was carefully added, the slurry was filtered through ' filter cel,' the dried (K_2CO_3) tetrahydrofuran was removed under reduced pressure and the residue was dissolved in chloroform (250 ml). The solution was washed with N-sodium hydroxide, water, and 2N-hydrochloric acid. The acidic washings were made alkaline with 10N-sodium hydroxide and extracted with methylene chloride. The extract was washed with saturated brine. Removal of the dried (K_2CO_3) methylene chloride layer and recrystallization (hexane–benzene) gave the *benzazepinol* (IIf) (4·9 g, 75%), m.p. 132—134° (lit.,[4] 132°) (Found: C, 73·55; H, 8·05. $C_{10}H_{13}NO$ requires C, 73·6; H, 8·05%).

2,3,4,5-*Tetrahydro*-3-*methyl*-1H-3-*benzazepin*-1-*ol* (IIg).—Compound (IIf) (5·0 g, 0·0307 mol) in 90% formic acid (8·1 g) was added to a 35—40% formaldehyde solution (2·7 ml). This mixture was warmed on a steam-bath for 6 h; then 3N-hydrochloric acid (13 ml) was added and the heating was continued for 20 min. The resulting solution was made strongly alkaline with 10N-sodium hydroxide and extracted with methylene chloride. The dried (K_2CO_3) extract was evaporated under reduced pressure and the resulting gum crystallized from hexane containing a small amount of benzene to give the *methylbenzazepinol* (IIg) (4·27 g, 78%), m.p. 98—99°; *picrate*, m.p. 179—181° (from EtOH) (Found: C, 50·55; H, 4·25; N, 13·5. $C_{17}H_{18}N_4O_8$ requires C, 50·25; H, 4·45; N, 13·8%).

1,2,3,4,5,6-*Hexahydro*-3-*benzazocin*-1-*ol* (IIh).—The alcohol (IIh), prepared from compound (IId) in the same manner that the azepine (IIf) was prepared from (IIc), was not isolated but was methylated as in the above experiment; overall yield 13·5%, m.p. 51—56°; *picrate* (EtOH), m.p. 202° (decomp.) (Found: C, 51·4; H, 4·85. $C_{18}H_{20}N_4O_8$ requires C, 51·45; H, 4·8%).

We thank the General Electric Co. and the Clarkson College of Technology Research Fund for support, and Dr. G. Proctor, Strathclyde University, for discussions and a sample.

[1/333 *Received, March 15th,* 1971]