matography was done with silica gel (70–230 mesh, product of E. Merck, Darmstadt).

Materials. Hexachlorocyclotriphosphazene (1) was obtained by ammonolysis of phosphorus pentachloride as previously reported[19] and purified by vacuum resublimation at 90–95 °C (0.5 mm); mp 113 °C.

1,1'-Dihydroxy-2,2'-binaphthyl (2) was synthesized and separated according to the method reported by Joffe[20] and recrystallized from benzene; mp 220 °C.

2,2'-Dihydroxy-1,1'-binaphthyl (3) was obtained by oxydation of 2-naphthol with ferric chloride[21] and purified by recrystallization from toluene; mp 219 °C.

Synthesis. (A) 3,3,5,5-Tetrachloro-1,1-(1,1'-dioxy-2,2'-binaphthyl)cyclotriphosphazene (4). A 34.8-g (0.1 mol) sample of hexachlorocyclotriphosphazene (1) and 28.6 g (0.1 mol) of 1,1'-dihydroxy-2,2'-binaphthyl (2) were dissolved on heating in dry benzene (700 mL). Then 50 mL (36.5 g, 0.36 mol) of triethylamine diluted with 50 mL of benzene was added dropwise over a 1-h period to the stirred solution of 1 and 2 at 50 °C. The reaction mixture was refluxed for 3–5 h to complete the reaction. The course of the reaction was followed by TLC analysis of aliquots with hexane–benzene (2:1) solvent, until the disappearance of the spot corresponding to 1. The complete conversion of 1 was then confirmed from the quantity of triethylamine hydrochloride formed in the reaction. The latter was filtered off hot under vacuum and determined by titration with 0.01 N AgNO₃. Removal of the solvents from the filtrate left a solid residue, which was washed several times with distilled water to remove traces of the amine hydrochloride, dried, and washed with cold acetone to remove traces of unreacted 2. Pure 4 was obtained by crystallization from benzene–hexane (1:1) to yield 43.7 g (76.3%) of white crystals: mp 310 °C; IR (Nujol mull) 3075 (C_{Ar}H), 1600, 1500 (Ar), 1250 (OC_{Ar}), 1205, 1185 (P=N), 1155, 1090 (POC_{Ar}), 950, 900, 840 (Ar), 880 (P=N) cm⁻¹; ¹H NMR (CDCl₃) 7.5–7.7 (m, 6 H), 7.8–8.0 (m, 4 H), 8.2–8.4 (m, 2 H) ppm; ³¹P NMR (see Table I); UV (cyclohexane) λ_{max} 215 nm (ϵ 3.9 × 10⁴), 259 (1.06 × 10⁵), 272 (3.1 × 10⁴), 283 (2.1 × 10⁴); mass spectrum (see Table II).

(19) S. M. Zhivukhin, V. V. Kireev, V. P. Popilin, and C. S. Kolesnikov, *Zh. Neorg. Khim.*, **14**, 1051 (1969).

(20) J. S. Joffe, *Zh. Obshch. Khim.*, **9**, 1136 (1939).

(21) Z. Dianin, *Ber. Dtsch. Chem. Ges.*, **6**, 1252 (1873).

(22) P. Diehl, E. Fluck, and R. Kosfeld, "NMR—Basic Principles and Progress", Springer-Verlag, Berlin, Heidelberg, and New York, 1971, p 104.

Anal. Calcd for $C_{20}H_{12}O_2Cl_4N_3P_3$: C, 42.80; H, 2.14; Cl, 25.30; N, 7.48; P, 16.30. Found: C, 42.63; H, 2.30; Cl, 25.50; N, 7.38; P, 16.45.

(B) 3,3,5,5-Tetrachloro-1,1-(2,2'-dioxy-1,1'-binaphthyl)-cyclotriphosphazene (5). A 34.8-g (0.1 mol) sample of hexachlorocyclophosphazene (1) and 28.6 g (0.1 mol) of 2,2'-dihydroxy-1,1'-binaphthyl (3) were subjected to the same procedure as described above for 4. The benzene-soluble product of the reaction was washed with distilled water and then dried to yield a pale yellow solid (49.2 g, 87.7%). This crude material was purified by column chromatography on silica with hexane–benzene (3:1). When the eluted fractions were allowed to stand overnight, compound 5 crystallized directly in the form of white, needlelike crystals: mp 283 °C; IR (Nujol mull) 3065 (C_{Ar}H), 1590, 1510 (Ar), 1260 (OC_{Ar}), 1215, 1190 (P=N), 1160, 1070 (POC_{Ar}), 995, 955, 915, 815 (Ar), 890 (P=N) cm⁻¹; UV (in cyclohexane) λ_{max} 216 nm ϵ 1.20 × 10⁵), 263 (7.4 × 10³), 305 (1.36 × 10⁴); ¹H NMR (CDCl₃) 7.2–7.6 (m, 8 H), 7.8–8.1 (m, 4 H) ppm; ³¹P NMR (see Table I); mass spectrum (see Table II).

Anal. Calcd for $C_{20}H_{12}O_2Cl_4N_3P_3$: C, 42.80; H, 2.14; Cl, 25.30; N, 7.48; P, 16.30. Found: C, 42.64; H, 2.72; Cl, 25.20; N, 7.27; P, 16.50.

The precipitate separated by the filtration of the reaction mixture (30.7 g) left a solid residue (3.2 g) after the amine hydrochloride was washed away. This was subsequently extracted with acetone, DMF, and chloroform. The remaining insoluble material (2.5 g, mp 313–320 °C) was found to consist mainly of **5,5-dichloro-1,1:3,3-bis(2,2-dioxy-1,1'-binaphthyl)cyclotriphosphazene (6).**

Analytically pure 6 was isolated chromatographically (0.2 g) from the main solvent-soluble fraction of the reaction products by stripping the chromatography column with benzene solvent: mp 330 °C; IR 3065, 1590, 1510, 1275, 1245, 1205, 1190, 1170, 1155, 1075, 995, 980, 955, 935, 900, 885, 835, 820 cm⁻¹ (the assignments are the same as for 5); UV (in cyclohexane) λ_{max} 219 nm (ϵ 2.21 × 10⁵), 263 (1.5 × 10⁴), 305 (2.8 × 10⁴); ³¹P NMR (see Table I); mass spectrum (70 eV), *m/e* (relative intensity) 773 (M⁺, 60.96), 775 ((M + 2)⁺, 40.96).

Anal. Calcd for $C_{40}H_{24}O_4Cl_2N_3P_3$: C, 61.80; H, 3.09; Cl, 9.17; N, 5.42; P, 12.0. Found: C, 61.30; H, 3.27; Cl, 9.13; N, 5.72; P, 11.83.

Registry No. 1, 940-71-6; 2, 604-60-4; 3, 602-09-5; 4, 72881-41-5; 5, 72866-26-3; 6, 72866-27-4.

New Synthesis of Diazepam

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An efficient preparation of 7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione from 5-chloro-*N*-methylisatoic anhydride and glycine has been devised, and from it, by the action of phenylmagnesium chloride on its *N*-acetyl derivative followed by treatment with hydroxylamine and cleavage of the resulting desacetyl oxime with sodium bisulfite, diazepam has been synthesized. The overall yield is about 50% from 5-chloroisatoic anhydride.

A new synthesis of diazepam has been devised. It depends critically on three new findings.

(1) 3,4-Dihydro-1*H*-1,4-benzodiazepine-2,5-diones, hitherto difficultly accessible,[1] can be made easily and in high yield directly from isatoic anhydrides and glycine. Intermediate in this preparation are *o*-aminohippuric acids,

which can be isolated as their difficultly soluble potassium salts or can be cyclized without isolation to the benzo-1,4-diazepine-2,5-diones.

To achieve these yields it is only necessary to add 1 equiv of a weak base (Na₂CO₃ or triethylamine) to convert the glycine into its anion in which the amino group is present

as the primary amine rather than as its ammonium ion. The optimum procedure makes use of triethylamine as the base and proceeds to 1 in 92% yield without the isolation of the intermediate.

(2) Although the action of phenylmagnesium halides or phenyllithium on 7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine is not smooth and does not yield useful products, the action of phenylmagnesium chloride on the corresponding 4-acetyl derivative 2,[2] available in very high (95%) yield by the action of acetic anhydride on 1, gives high yields (81%) of 5-chloro-2-[(*N*-acetylglycyl)methyl-amino]benzophenone (3). A small amount (9-12%) of 1 also appears to be produced, presumably by attack of the Grignard reagent on the *N*-acetyl group.[3]

(3) Although the action of alkaline reagents on 3 leads primarily to 6-chloro-4-phenyl-3-aminoquinol-2-one derivatives, treatment of 3 with excess hydroxylamine hydrochloride in pyridine leads to deacetylation and produces the oxime of the deacetyl compound 4 in high yields (87-89%). The deacetyl compound is readily separated from other components of the reaction mixture by making use of its solubility in dilute acid.

Diazepam is produced in high yield (91.7% crude) from 4 by the action of aqueous alcoholic NaHSO$_3$.[4]

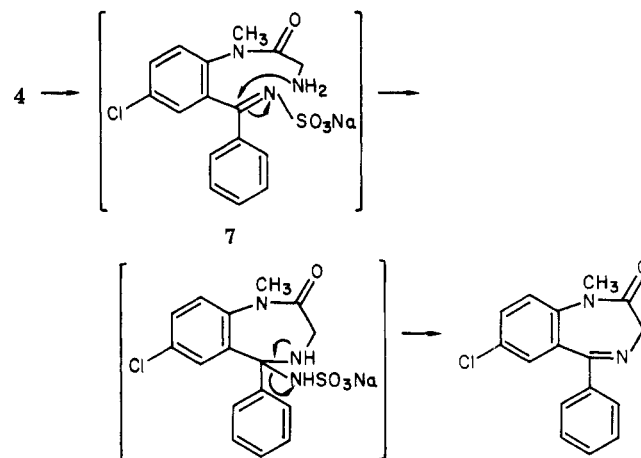Overall, the synthesis proceeds as in Scheme I.

The overall yield from commercially available 5-chloroisatoic anhydride is 50-51%. The crude diazepam obtained, although a bit off color, is of good quality (mp 129-131.5 °C) without further purification, and the process proceeds from 1 to diazepam without purification of any of the intermediates beyond the counter-current removal of 1 from crude 3.

It is not obvious that the conversion of 4 to diazepam proceeds through the ketone 5, an intermediate in earlier syntheses of diazepam. Some indication that it may *not* go through 5 is provided by the observation that 4 can be converted into diazepam by NaHSO$_3$ under *anhydrous* conditions, which would appear to preclude 5 as an intermediate. The yield, however, is lower than when the

5
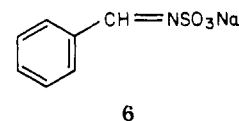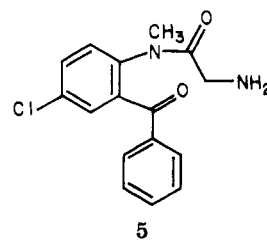
reaction is carried out in aqueous alcoholic NaHSO$_3$. In view of the facts that the action of sulfur dioxide on hydroxylamine and on simple oximes gives sulfamic acid, H$_2$NSO$_3$H,[5] and that von Pechmann[6] isolated from the action of NaHSO$_3$ on benzaldoxime a crystalline substance, C$_7$H$_7$NS$_2$O$_6$Na$_2$·3H$_2$O, which he regarded as the bisulfite addition product of 6, it seems probable that 7 is an in-

6

termediate in this transformation and yields diazepam directly without going through the ketone 5. Intramo-

7

lecular nucleophilic attack by the amino group on the imino group followed by loss of sodium sulfamate seems at least as likely as intermolecular attack by water to give the ketone 5.

We do not regard the formation of the bisulfite addition product of heptaldehyde by the action of NaHSO$_3$ on heptaldoxime[4] as indicating the intermediacy of this bisulfite addition product in the cleavage of the oxime by bisulfite, inasmuch as it could easily have been formed subsequently from the heptaldehyde produced.

Diazepam can also be prepared directly from 3 by the action of methanolic sulfuric acid, but the yield is lower (52.5%), and the product must be isolated as its sparingly soluble perchlorate. 5-Chloro-2-(methylamino)benzophenone is also produced in this reaction (21%). The formation of aminoquinolones from substances similar to

(1) P. M. Carabateas and L. S. Harris [*J. Med. Chem.*, 9, 6 (1966)] obtained only 20% of 3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione from the interaction of isatoic anhydride and glycine ethyl ester, and A. Ermili and G. Filacchione [*Ann. Chim. (Rome)*, 59, 770 (1969)] report a similar yield from isatoic anhydride and glycine. M. Uskoković, J. Iacobelli, and W. Wenner [*J. Org. Chem.*, 27, 3606 (1962)] were able to cyclize *o*-aminohippuric acid piperidide to the benzodiazepinedione quantitatively, but the piperidide was obtained in only 50% from the corresponding ethyl ester, itself not easily obtainable in high yield [K. Miyatake and S. Kago, *Yakugaku Zasshi*, 72, 1160 (1952)]. As recently as 1975, a preparation of 3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione giving a 53% yield was reported as an "improved synthesis" [D. H. Kim, *J. Hetrocycl. Chem.*, 12, 1323 (1975)]. The route from methyl *N*-(haloacetyl)-anthranilate derivatives by reaction with ammonia and amines claimed by Uskoković and Wenner (U.S. Patent 3 244 698) and by Griot (British Patent 1 145 471 and other patents in this series) is difficult to assess, since in none of these patents is the yield given. Uskoković, Iacobelli, and Wenner state, however (loc. cit.), that "attempts were first directed to the ring closure of N-(haloacetyl)anthranilate esters and amide with ammonia and other bases, but in every case the products were quinazolin-4-(3*H*)-ones".

(2) The structure of 2 and the course of its subsequent reaction with phenylmagnesium chloride are both demonstrated by the identity of the product 3 of the latter reaction with the product of the action of aceturoyl chloride with 5-chloro-2-(methylamino)benzophenone.

(3) On a small laboratory scale, 1 can be separated from 3 quite efficiently by making use of the greater solubility of 1 in water. A counter-current extraction scheme using separatory funnels and distributing 1 and 3 between benzene and water allows 1 to be isolated. Acylation of the 1 recovered reconverts it to starting 2 in very high yield. It seems likely that on a larger scale a system of counter-current columns could be devised to carry out this separation efficiently.

(4) S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, 31, 3446 (1966).

(5) M. Schmidt, *J. Prakt. Chim.*, 44, 513 (1891); F. Raschig, *Justus Liebigs Ann. Chem.*, 241, 161 (1887); H. H. Sisler and L. F. Audrieth, *J. Am. Chem. Soc.*, 61, 3389 (1939).

(6) H. von Pechmann, *Ber. Dtsch. Chem. Ges.*, 20, 2539 (1887).

3 is well-known,[7] and more complex acyl derivatives related to **3** have been converted to diazepam.[8]

A number of other acyl derivatives of **1** have also been prepared (trifluoroacetyl, propionyl, *n*-butyroyl, and isobutyroyl, all in very high yield). The trifluoroacetyl derivative of **1** was studied with the expectation that the trifluoroacetamide analogue of **3** would offer more chance for selective hydrolysis or methanolysis than **3** itself, but the action of phenyl Grignard reagents on it is less smooth and in particular produces larger quantities of **1**, presumably by attack of the Grignard reagent on the carbonyl of the trifluoroacetamide group.

The more highly substituted acyl derivatives of **1** (propionyl, *n*-butyroyl, and isobutyroyl) are attacked by phenylmagnesium chloride more selectively at the C_5 carbonyl than is **2**, and, in particular, the isobutyroyl derivative **8** is attacked at C_5 exclusively, giving rise to nearly quantitative yields of the corresponding ketone **9**.
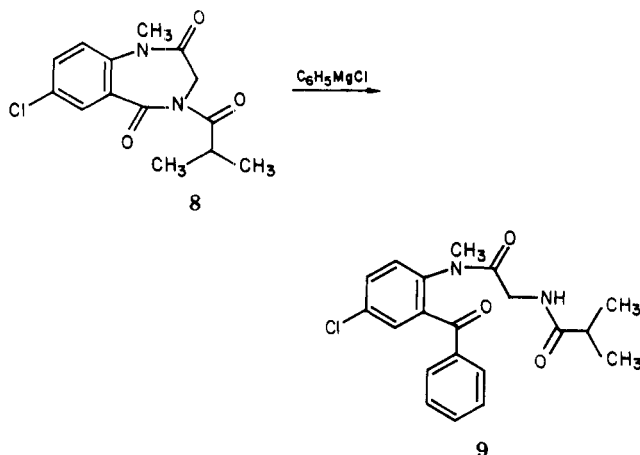
Unfortunately, the conversion of **9** and the corresponding propionyl and *n*-butyroyl derivatives to diazepam either by the hydroxylamine cleavage route or by acid-catalyzed methanolysis is less satisfactory, and the best overall results appear to be obtained with the acetyl derivative **2**.

The condensaton of alanine with 5-chloro-2-*N*-methylisatoic anhydride is less smooth than that of glycine, and, in particular, more of the byproduct 5-chloro-*N*-methylanthranilic acid is produced. It seems possible that this reaction will proceed really well only with glycine. Acetylation of the 3-methyl analogue of **1** is also somewhat less satisfactory.

Experimental Section

All melting points are corrected unless otherwise specified. Thin-layer chromatograms were done on silica gel developed with chloroform–methanol (10:1) unless otherwise specified. IR spectra were recorded on a Perkin-Elmer Infracord spectrometer and NMR spectra on a Jeolco MH-100 NMR spectrometer. Analyses were carried out by Chemalytics and Galbraith Laboratories.

5-Chloro-*N*-methylisatoic anhydride was prepared from commercially available 5-chloroisatoic anhydride by methylation with methyl iodide in the presence of dimethylformamide and sodium carbonate, according to Palazzo and Silvestrini.[9] These authors report a 72% yield, but we have had no difficulty in obtaining 85% yields by their procedure. Crystallized from acetic acid, it melts at 201–203 °C (yield 85.2%).

7-Chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (1). (a). A mixture of finely ground 5-chloro-*N*-methylisatoic anhydride (5.19 g), 2.25 g of glycine, 4.15 mL of practical-grade triethylamine, and 30 mL of water was stirred at room temperature for 5 h. All solid material had disappeared after 3.5–4 h. Volatile material was removed as completely as possible on a rotary evaporator (bath temperature 80 °C), and the residue was treated with 60 mL of glacial acetic acid and heated to reflux for 4.5 h. After the mixture cooled, as much acetic acid as possible was removed on a rotary evaporator, and the tan oily residue was treated with 30 mL of ether. On brief swirling of the mixture crystallization set in, and the colorless crystalline material was collected after standing overnight and was washed with ether: 4.60 g; mp 176.5–178 °C.[10]

The ethereal filtrate (two phases) was diluted with enough ethyl acetate to render it homogeneous, washed twice with dilute sodium carbonate and then with water, filtered through anhydrous sodium sulfate, and concentrated. Recrystallization of the crystalline residue (0.53 g) gave 0.43 g of product: mp 177–179 °C; total yield 5.03 g (91.8%).

The carbonate extracts were just acidified to congo red, precipitating a grayish green crystalline material (0.11 g, air-dried, mp 178–180 °C) which after recrystallization from ethyl acetate gave bold yellow prismatic needles: 0.076 g (1.7%); mp 182–183.5 °C; mixture melting point with authentic 5-chloro-*N*-methylanthranilic acid (mp 181–183.5 °C) was 181–183 °C (lit.[11] mp 173 °C).

(b). A similar reaction using sodium carbonate in place of triethylamine gave, from 4.24 g of 5-chloro-*N*-methylisatoic anhydride, 3.59 g (80%) of **1**, mp 179–180.5 °C.

(c). 5-Chloro-2-(methylamino)hippuric Acid, Its Potassium Salt, and Their Conversion to 1. A mixture of finely ground 5-chloro-*N*-methylisatoic anhydride (4.24 g), 2.25 g of glycine, 3.18 g of sodium carbonate, and 30 mL of water was stirred in an ice bath overnight. Very brief warming was sufficient then to give a clear solution. To this solution was added 5 g of potassium acetate in 5 mL of water. Rapid precipitation of a pale yellow solid occurred. The solution was heated to bring this solid into solution, and crystallization was then allowed to take place eventually in an ice chest. The pale yellow crystalline solid was collected and washed with 15 mL of 10% potassium acetate to yield **potassium 5-chloro-2-(methylamino)hippurate**: 4.95 g; mp 332–335 °C (profound decomposition); yield 88.5%. A small sample was recrystallized from water for analysis.

Anal. Calcd for $C_{10}H_{10}ClN_2O_3K$: C, 42.78; H, 3.59; N, 9.98. Found: C, 42.64; H, 3.54; N, 9.95.

Acidification of the filtrate just to congo red gave 0.34 g (7%) of 5-chloro-*N*-methylanthranilic acid as pale yellow needles (mp 176–180 °C) which after recrystallization from methyl acetate melted at 181–183 °C.

Acidification of a suspension of 2.00 g of the above potassium salt in 10 mL of water with dilute hydrochloric acid until the suspension was just acid to congo red gave 1.64 g (air-dried) of crude **5-chloro-2-(methylamino)hippuric acid** with gas evolution: mp 163–165 °C; yield 94.8% from the potassium salt or 83.9% from 5-chloro-*N*-methylisatoic anhydride. A small sample was recrystallized several times for analysis (gas evolution); mp 168–170 °C.

Anal. Calcd for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; N, 11.54. Found: C, 50.50; H, 4.49; N, 12.04.

When this acid was first obtained, it melted at 129–131 °C, but on standing for several months this sample had become opaque and then melted at 163–166 °C (gas evolution). All subsequent preparations had the higher melting point.

Heating this acid (1.57 g) in 20 mL of glacial acetic acid for 4.5 h and processing as in procedure b above gave 1.38 g of **1**: mp 178–180.5 °C; 95% yield from the acid or 79.5% from 5-chloro-*N*-methylisatoic anhydride.

The potassium salt (2.00 g) was also converted directly to **1** by refluxing in 25 mL of glacial acetic acid for 4.5 h. Processing as in b above gave 1.52 g (95%) of **1**, mp 176–178 °C. Recrys-

(7) S. C. Bell et al., *J. Org. Chem.*, **27**, 562 (1962); L. H. Sternbach, et al., *ibid.*, **27**, 3788 (1962); R. I. Fryer et al., *J. Chem. Soc.*, 3097 (1964).

(8) A. Stempel and N. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962); S. C. Bell et al., *ibid.*, **27**, 562 (1962); R. I. Fryer et al., *J. Chem. Soc.*, 3097 (1964); Delmar Chemicals Ltd., The Netherlands Patent 6 500 446; F. H. McMillan and I. Pattison, French Patent 1 394 287.

(9) G. Palazzo and B. Silvestrini, U.S. Patent 3 409 668.

(10) Reported melting points of 171.5–173.5 °C (M. Uskokovic and W. Wenner, U.S. Patent 3 244 698) and 178–179 °C (R. G. Griot British Patent 1 145 471.

(11) O. Keller, *Arch. Pharm. (Weinheim, Ger.)*, **246**, 37 1913.

tallization from ethyl acetate gave 1.31 g of product, mp 179.5–181 °C; an additional 0.10 g (mp 178–180 °C) was obtained by reworking the mother liquors, for a total yield of recrystallized material of 1.41 g (88%) from the potassium salt or 78% from 5-chloro-*N*-methylisatoic anhydride).

7-Chloro-1,3-dimethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione resulted from a similar experiment using 5-chloro-*H*-methylisatoic anhydride and *dl*-alanine. A mixture of 4.48 g of finely ground 5-chloro-*N*-methylisatoic anhydride, 2.18 g of *dl*-alanine, 3.46 mL of practical-grade triethylamine, and 30 mL of water was stirred for 18 h at room temperature. The solution had nearly completely cleared after 5 h. As much water as possible was removed at the rotary evaporator, and the light tan heavy oily residue was heated under reflux for 4.5 h with 50 mL of glacial acetic acid. Removal of the acetic acid under diminished pressure gave a residue which crystallized spontaneously. It was diluted with ether, collected, and washed with ether: yield 3.26 g; mp 198–206 °C.

Recrystallization of this material from ethyl acetate and a little alcohol (sparingly soluble in ethyl acetate alone) and reworking of all filtrates gave a total of 2.09 g (44%) of product, mp 210.5–211.5 °C.

A small sample was recrystallized from ethyl acetate for analysis: NMR δ 1.4 (d), 3.15 (s), 3.8 (q), 7.0–7.8 (arom) 7.9 (br s); mp 210.5–211.5 °C; colorless small leafs.

Anal. Calcd for C₁₁H₁₁ClN₂O₂: C, 55.35; H, 4.65; N, 11.74. Found: C, 55.67; H, 4.47; N, 11.82.

Extraction of the combined filtrates with dilute sodium carbonate and acidification of the extracts just to congo red gave 1.16 g of crude acidic material, from which by crystallization from ethyl acetate 0.82 g (22%) of 5-chloro-*N*-methylanthranilic acid was obtained. Thin-layer chromatography showed the presence of another acid, possibly 5-chloro-2-(*N*-methylamino)benzoylalanine.

7-Chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione was prepared in an analogous way. A mixture of 5-chloroisatoic anhydride (3.94 g of 97% pure commercial product), 1.87 g of glycine, 30 mL of water, and 3.46 mL of triethylamine was stirred at room temperature for 4 h. The completely homogeneous solution was concentrated as much as possible on a rotary evaporator, and the tan oily residue was heated to reflux with 50 mL of glacial acetic acid for 4.5 h. On concentration on the rotary evaporator, crystalline material began to separate (in some runs, crystalline material separated during the reflux period). The partially concentrated suspension was allowed to stand at room temperature overnight, and then the crystalline material was collected and washed with ether: 3.05 g (72.6%); mp 325–328 °C dec¹² (uncor).

4-Acetyl-7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (2). A mixture of 1 (1.00 g) and 3 mL of acetic anhydride was heated to reflux in a Craig tube for 2.5 h. The original suspension went into solution more or less rapidly; after about 1 h crystalline material began to separate and was cooled, allowed to stand overnight, and collected: 1.12 g (94%); mp 207–208.5 °C; colorless prismatic blades.

A further 13 mg (mp 205.5–207 °C) was obtained by hydrolysis of the filtrate and recrystallization of the resulting solid from acetic anhydride [total yield 1.13 g (95%)]. A small sample was recrystallized from acetic anhydride for analysis: mp 207.5–209 °C; IR 5.94, 6.02 μm; mass spectrum, *m/e* 266 (M⁺), 251, 223, 167, 139; NMR δ 2.50 (s), 3.60 (s), inter alia.

Anal. Calcd for C₁₂H₁₁ClN₂O₃: C, 54.05; H, 4.16; N, 10.50. Found: C, 54.35; H, 4.21; N, 11.11.

4-(Trifluoroacetyl)-7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione. A mixture of 672 mg of 1 and 10 mL of trifluoroacetic anhydride was heated to reflux for 30 min. The suspended 1 went into solution rapidly, and a colorless crystalline precipitate soon formed. The mixture was cooled, and the crystalline material was collected and dried in air (801 mg; mp 176–178 °C with some preliminary softening). The residue obtained by evaporation of the filtrate was crystallized from ethyl acetate to give 91 mg of recovered 1, mp 176.5–177.5 °C. The yield based on 1 not recovered was 96.3%.

In spite of the similarity in melting points, 1 and the trifluoroacetyl derivative differ substantially in properties. The latter shows a parent ion peak at *m/e* 320 and other prominent peaks at *m/e* 300, 291, 264, 251, 223, 195, 167, 139, and 112. It is notably unstable and gums up on standing for several days when exposed to the air. Its melting point after standing for some time drops to ca. 140–160 °C. It was not obtained in analytically pure condition and seemed to be contaminated with small amounts of acidic impurities (trifluoroacetic acid?): NMR δ 3.45 (s), 4.6 (br s), inter alia; IR 5.72, 5.80, 5.90 μm.

Anal. Calcd for C₁₂H₈ClF₃N₂O₃: O=CCF₃, 30.26. Found (by hydrolysis with standard base): O=CCF₃, 31.26.

4-Acetyl-7-chloro-1,3-dimethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione. 7-Chloro-1,3-dimethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (500 mg) was heated to reflux for 5 h with 3 mL of acetic anhydride. Most of the excess acetic anhydride–acetic acid was allowed to evaporate at the boiling point, until somewhat less than 1 mL of solution remained, and the residue was allowed to crystallize in an ice box. Colorless prisms (551 mg, mp 160–164.5 °C) were obtained. Recrystallization from methanol–CH₂Cl₂ gave 448 mg (82%) of product: mp 165–166 °C; NMR δ 1.08 (br d), 2.62 (s), 3.4 (s), 5.95 (vbr s), inter alia.

Anal. Calcd for C₁₃H₁₃ClN₂O₃: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.79; H, 4.65; N, 10.06.

4-Propionyl-7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione. The propionyl derivative of 1 was prepared similarly. A mixture of 1 (1.00 g) and 8 mL of propionic anhydride was heated in a bath maintained at 140 °C for 4.25 h and then poured into ice and allowed to stand overnight. The initial insoluble oil had by this time granulated to a crystalline solid which was collected and washed well with water and allowed to dry in air: 1.19 g (96%); mp 155.5–157 °C; NMR δ 1.20 (t), 3.1 (diffuse q), 3.4 (s), 3.82 (very diffuse s), 5.25 (very diffuse s), inter alia. A small sample was recrystallized twice from methanol for analysis; mp 158–158.5 °C.

Anal. Calcd for C₁₃H₁₃ClN₂O₃: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.83; H, 4.87; N, 9.96.

4-*n*-Butyroyl-7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione. The *n*-butyroyl derivative of 1 was prepared as described above for the propionyl derivative. From 1.00 g of 1 and 8 mL of *n*-butyric anhydride, 1.25 g (95%) of crude butyroyl derivative (mp 133–134.5 °C) was obtained. A small sample was recrystallized twice from ethyl acetate–cyclohexane for analysis; mp 136.5–137 °C.

Anal. Calcd for C₁₄H₁₅ClN₂O₃: C, 57.05; H, 5.13; N, 9.51. Found: C, 57.49; H, 5.26; N, 9.54.

4-Isobutyroyl-7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (8). The isobutyroyl derivative of 1 was prepared similarly. From 500 mg of 1 and 5 mL of isobutyric anhydride heated for 5 h, 590 mg (90%) of crude isobutyroyl derivative (mp 108–109.5 °C) was obtained. Hydrolysis of excess anhydride was slower in this case, and the quenched reaction mixture was allowed to stand with occasional stirring for 2 days before collection of the product. A small sample was crystallized twice from ethyl acetate–cyclohexane for analysis: mp 111–112.5 °C; NMR δ 1.1 (d), 3.2 (s), 3.7 (m), 3.7 and 5.05 (very diffuse s), inter alia.

Anal. Calcd for C₁₄H₁₅ClN₂O₃: C, 57.05; H, 5.13; N, 9.51. Found: C, 57.44; H, 5.32; N, 9.48.

Action of Phenylmagnesium Chloride on 2. 5-Chloro-2-(aceturoylmethylamino)benzophenone (3). A suspension of finely ground 2 (483 mg, 1.82 mmol) in 12 mL of tetrahydrofuran, freshly refluxed with and distilled from lithium aluminum hydride, was treated slowly over 20 min with stirring with 1.00 mL (2.18 mmol, 1.20 equiv) of 2.18 N commercial (Fisher) phenylmagnesium chloride at room temperature (15–18 °C). During the addition the tip of the delivery syringe was kept below the surface of the stirred solution. During the addition the solution becomes deep red, and the suspended 2 goes into solution. Stirring was continued for 1.5 h after the addition was complete, during which the color lightens to a clear bright yellow.

The reaction mixture was treated with ammonium chloride solution and extracted four times with CH₂Cl₂, the extracts were filtered through anhydrous Na₂SO₄ and concentrated, and the residue was pumped out at 100 °C and reduced pressure to give

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(12) Reported melting point of 327–327.5 °C (M. Uskoković, J. Iacobelli, and W. Wenner¹).

684 mg of yellow glass. This material consists predominantly of **3** with small amounts of **1** (the ratio by weight of **3** to **1** was 10.8 as determined by high-pressure LC; in other runs this ratio varied between 7 and 10). It also contains about 13 mg of biphenyl, a contaminant of the Grignard reagent, 11 mg of 5-chloro-2-(methylamino)benzophenone,[13] and a small amount of starting material (ca. 2–3%), as well as other substances.

This material was subjected to a 3 × 14 counter-current distribution scheme using benzene (3 × 20 mL) and water (14 × 20 mL) in separatory funnels. From the three 20-mL benzene fractions on concentration was obtained 568 mg of a yellow glass after pumping. A semipreparative assay of this by high-pressure LC showed it to be 88.2% **3** (500 mg) with no detectable **1**. The 14 20-mL water fractions, combined and extracted six times with 25 mL of CH_2O_2, yielded from the CH_2Cl_2 extracts 77 mg of crude **1** shown by high-pressure LC to contain 70 mg of **1**. This crude **1** was heated to reflux with 0.8 mL of acetic anhydride for 2.25 h, evaporated to ca. 0.3 mL, and allowed to crystallize to give 69 mg of **2** (mp 203.5–206 °C) which after recrystallization from acetic anhydride gave 65 mg of recovered **2**, mp 207–209 °C.[14]

The yield of **3** (500 mg by assay) on the basis of starting material not recovered (483 − 65 = 418 mg) was 92%. In other runs, the assay of **3** varied between 77 and 88%.

If the Grignard reaction mixture is heated or stirred for long periods of time, appreciable quantities of the cyclization product **6-chloro-1-methyl-4-phenyl-3-acetylaminoquinol-2-one** are produced. A suspension of 532 mg of finely ground **2** in 15 mL of tetrahydrofuran was heated to reflux and treated dropwise with 1.00 mL of 2.18 N phenylmagnesium chloride in the tetrahydrofuran. Refluxing was continued for 1.5 h. Processing of the reaction mixture as described above gave 641 mg of dark yellow glass. High-pressure LC of this material showed a large peak corresponding to **1** and a small peak corresponding to **3**, but the largest peak was at appreciably longer retention time than that of either **2** or **3**. A 3 × 10 counter-current distribution of the sort described above gave from the benzene fractions 441 mg of dark yellow glass whose high-pressure LC showed the presence of **3**, **1**, and the peak of long retention time in a molar ratio of 1:3:15, and from the water fractions was isolated 182 mg of colorless crystalline material [mp 166–172 °C (impure **1**)] which on refluxing for 2.5 h with acetic anhydride gave 182 mg of **2**, mp 207–208.5 °C.

The benzene fractions (441 mg) crystallized readily under ethyl acetate and on recrystallization from ethyl acetate and a trace of acetic acid gave 171 mg of 6-chloro-1-methyl-4-phenyl-3-(acetylamino)quinol-2-one mp 230–232.5 °C. Two further crystallizations raised the melting point to 232–233.5 °C: NMR δ 1.92 (2), 3.8 (s), inter alia; UV 217 241, 287, 332 (sh), 345, 360 (sh) nm. mass spectrum, m/e 326 (M⁺). This substance is also produced in smaller amounts if the reaction between **2** and phenylmagnesium chloride is allowed to stir for long periods (24 h) at room temperature.

(13) The absorption maximum of this substance at 412 nm (ε 6950), a wavelength at which other components of this mixture are transparent, can conveniently be used to determine it.

(14) On the assumption that the **1** present in this reaction mixture arises from attack of phenylmagnesium chloride on the acetyl carbonyl group of **2**, one would expect to find an approximately equivalent amount of $(C_6H_5)_2C(OH)CH_3$ formed by the sequence:
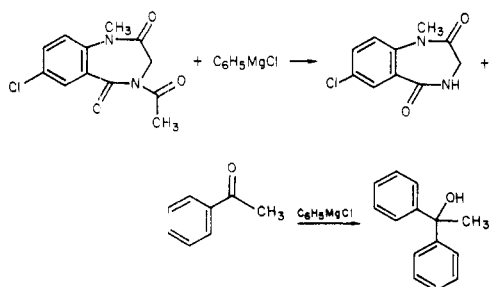
We have not identified this substance in the product, whose NMR does show an extraneous shoulder at δ 1.90, the same as that reported for this substance ("Aldrich Library of NMR Spectra", Vol. 5, Aldrich Chemical Co., Milwaukee, WI, 1974, p 40.)

Scheme I
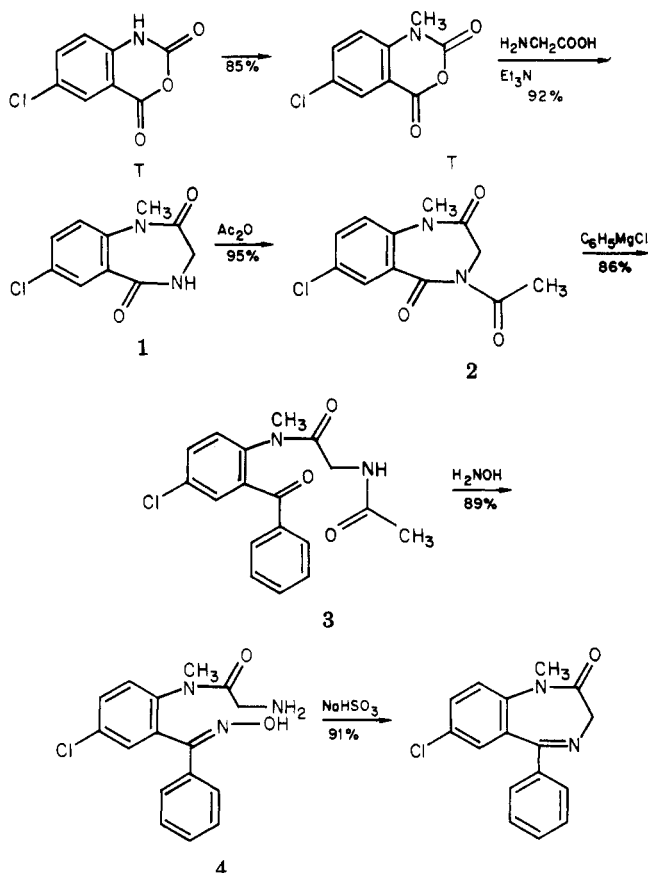
Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.40; H, 4.83; N, 8.58.

The action of sodium hydroxide in methanol on **3** also gives rise to this substance as well as the corresponding deacetyl compound. Crude **3** (182 mg) in 5 mL of methanol and one pellet of KOH were heated to reflux for 3.75 h, cooled, diluted with water, and extracted four times with CH_2Cl_2. The extracts were washed with water, filtered through anhydrous Na_2SO_4, concentrated, and pumped out to give 137 mg of pale yellow glass. This was separated by thick-layer chromatography into three fractions: (a) 5 mg of yellow crystalline material traveling near the solvent front, impure 5-chloro-2-(methylamino)benzophenone; (b) 80 mg of nearly colorless glass which crystallized on standing and after several recrystallizations melted at 140–141 °C [mass spectrum m/e 284 (M⁺); UV 235, 256 (sh), 334, 348 nm; this material, on the basis of its UV,[15] appears to be **6-chloro-1-methyl-4-phenyl-3-aminoquinol-2-one** (lit.[15] mp 130–133 °C)]; (c) 44 mg of colorless glass which crystallized spontaneously [mp 232–233.5 °C] after crystallization from ethyl acetate; mass spectrum, m/e 326 (M⁺); UV 217, 241, 287, 332 (sh), 345, 360 (sh) nm; **6-chloro-1-methyl-4-phenyl-3-(acetylamino)quinol-2-one**].

Compound **3**, when pure, is crystalline, but it crystallizes poorly and is difficult to purify. For conversion to **4**, material of the above quality was used.

A small sample purified by thick-layer chromatography followed by distillation at 10^{-3} mm (bp 190–210 °C) crystallized on standing (mp 106–111 °C) and was unchanged by recrystallization from ethyl acetate: very pale yellow prisms; NMR δ 1.94 (s), 3.0, 3.2 (conformationally split s), 3.8 (qd); mass spectrum, m/e 344 (M⁺).

Anal. Calcd for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; N, 8.13. Found: C, 63.12; H, 5.23; N, 8.25.

The action of aceturoyl chloride on 5-chloro-2-(methylamino)benzophenone also gives rise to **3**. Aceturoyl chloride[16] (900 mg) was suspended in 7 mL of CH_2Cl_2 and treated portionwise at room temperature with 1.00 g of 5-chloro-2-(methy-

(15) R. I. Freyer, B. Brust, and L. H. Sternbach [*J. Chem. Soc.*, 3097 (1964)] report UV 235, 255 (sh), 332, and 349 nm for the corresponding demethyl compound.

(16) J. Max, *Justus Liebegs Ann. Chem.*, **369**, 276 (1909).

lamino)benzophenone, and the mixture was allowed to stand (with occasional swirling at first) overnight. The yellow color of the ketone had faded completely within 2 h. After dilution with more CH_2Cl_2, the mixture was washed twice with water, filtered through anhydrous Na_2SO_4, concentrated, and pumped out at reduced pressure to give 1.45 g (1.41 g theoretical) of very pale yellow glass which crystallized slowly when seeded; mp 106–111 °C. Its IR and NMR spectra were indistinguishable from those of the sample described above.

Action of Phenylmagnesium Chloride on the N-Isobutyroyl Derivative 8. 9. A sample of the N-isobutyroyl derivative 8 (294 mg) in 8 mL of tetrahydrofuran, freshly distilled from lithium aluminum hydride, was cooled to –78 °C and treated dropwise with stirring with 0.47 mL (1.03 equiv) of 2.18 N phenylmagnesium chloride in tetrahydrofuran. The mixture was stirred for 5.5 h, during which the bath temperature rose gradually to room temperature.

The reaction mixture was treated with dilute ammonium chloride and partitioned between ether and the aqueous solution (two ether extractions). The ether layers were washed with brine, filtered through anhydrous Na_2SO_4, and concentrated to give, after pumping, 400 mg (107%) of pale yellow glass. High-pressure LC of this material shows no 1 in contrast to runs with N-trifluoroacetyl, -acetyl, -propionyl, and -n-butyroyl derivatives, which show 1 in amounts decreasing with this sequence. Traces of two other substances, one of which is starting material, are detectable. Little or no 5-chloro-2-(methylamino)benzophenone is present as assayed by the UV spectrum of several solvent-front fractions of high-pressure LC injections.

Its NMR shows a doublet at δ 1.1 and a multiplet at δ 2.4 as well as a conformationally split singlet at δ 3.1, consistent with the isobutyroyl analogue of 3.

Analogous Grignard reactions with the corresponding N-propionyl and N-n-butyroyl derivatives 1 gave comparable results, although the amount of 1 produced was larger with the N-propionyl derivative and easily discernible (high-pressure LC) with the N-butyroyl derivative. The NMR spectra of both were consistent with structures analogous to that of 3.

Action of Hydroxylamine on 3. Oxime of 5-Chloro-2-(glycylmethylamino)benzophenone (4). Crude 3 (568 mg) directly from the counter-current distribution described above (assay 500 mg 3) and 485 mg of hydroxylamine hydrochloride were heated in 10 mL of pyridine under N_2 in a bath maintained at 70 °C for 45 h. The pyridine was removed as completely as possible on a Rotovap, the residue was taken into ether–3% HCl, the layers were separated, and the ether layer was extracted three more times with 3% HCl. The combined acid extracts were washed four times with CH_2Cl_2, the CH_2Cl_2 washes back-washed once with 3% HCl, and the combined 3% HCl extracts made basic to excess with ammonia. The liberated basic material was taken into CH_2Cl_2 (four extractions), filtered through anhydrous Na_2SO_4, concentrated, and pumped out to yield 259 mg of 4 as a nearly colorless glass which crystallized spontaneously; mp 202–204 °C.

The original ether raffinate and the CH_2Cl_2 washes of the 3% acid solution were combined, filtered, and concentrated to yield 248 mg of yellow glass whose TLC showed it to contain quite a bit of unchanged 3. It was heated under N_2 with 210 mg of hydroxylamine hydrochloride in 7 mL of pyridine at 70 °C for 43.5 h as above. A similar workup yielded 106 mg more of 4 (mp 201–203.5 °C) and 122 mg of acid-insoluble material. A third repetition of this cleavage on this last sample gave an additional 13 mg of 4 [crystalline, total yield 378 mg (82.2% on the basis of the content of 3 in the crude starting material; in other runs yields as high as 88% were obtained)] as well as 106 mg of yellow glass whose TLC and high-pressure LC showed it to consist largely of one of the oximes of 5-chloro-2-(methylamino)benzophenone.

Compound 4, when crystalline, is sparingly soluble in most organic solvents (although extraction into CH_2Cl_2 of the crude material precipitated by ammonia has presented no problems at least on a small scale). Another sample was purified by crystallization several times from methanol; mp 212–213 °C; colorless.

Anal. Calcd for $C_{16}H_{16}ClN_3O_2$: C, 60.47; H, 5.08; N, 13.22; Cl, 11.16. Found: C, 60.16; H, 5.10; N, 12.84; Cl, 10.80.

Its NMR spectrum no longer shows the acetyl methyl singlet but only the NCH_3 signal at δ 2.7–2.8, which as in all open-chain substances in this series shows unequal conformational splitting.

Its mass spectrum shows little or no parent ion peak but does show a large peak at m/e 299 ($M^+ - H_2O$).

The 106 mg of neutral material was cleaved by refluxing with 500 mg of $NaHSO_3$ and 5 mL each of alcohol and water for 17.5 h. Removal of most of the alcohol at reduced pressure and distribution of the aqueous residual suspension between ether and water gave from the ether fraction, after drying and concentrating, 89 mg of yellow glass which crystallized spontaneously. A UV assay, making use of the maximum at 412 nm, showed this material to contain 52 mg of 5-chloro-2-(methylamino)benzophenone. Recrystallization from methanol gave 5-chloro-2-(methylamino)benzophenone: 44 mg; bright yellow blades; mp 93–95.5 °C; its mixture melting point with an authentic sample (mp 96.5–97.5 °C) was 94.5–97 °C.

When this hydroxylamine cleavage reaction is carried out with smaller amounts of hydroxylamine hydrochloride or for shorter periods of time, modest yields of the **oxime of 5-chloro-2-(aceturoylmethylamino)benzophenone** (the oxime of 3) can be obtained: mp 220–221 °C dec, after several crystallizations from pyridine–ethyl acetate; sparingly soluble in common organic solvents.

Anal. Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.08; H, 5.04; N, 11.68; Cl, 9.85. Found: C, 60.23; H, 4.67; N, 11.86; Cl, 9.31.

Its NMR spectrum in deuterated Me_2SO shows two methyl signals, one at δ 2.28 and the other at δ 1.77. Like that of 4, its mass spectrum shows no parent ion but has a strong signal at m/e 341 ($M^+ - H_2O$).

Action of $NaHSO_3$ on 4. Diazepam. Crude 4, as obtained in the above experiment (378 mg), was refluxed for 12 h with 1.13 g of $NaHSO_3$ in a mixture of 15 mL of alcohol and 7.5 mL of water. Most of the alcohol was removed on a rotary evaporator, and the residue was treated with ether and 3% HCl. The ether layer was washed three additional times with 3% HCl, and then the combined acid fractions were extracted five times with CH_2Cl_2. The extracts were filtered through anhydrous $NaSO_4$ and concentrated. The orange yellow residue (303 mg, 89.3%, after thorough drying) crystallized readily on seeding with diazepam and had a melting point of 129–131.5 °C; its mixture melting point with a sample of pure diazepam (mp 132–133 °C) was 128.5–131.5 °C. Its NMR spectrum is virtually indistinguishable from that of authentic diazepam and, in particular, shows the very characteristic splitting of the methylene protons observed by Lehn.[17] Its IR spectrum is indistinguishable from that of diazepam.

Action of Methanolic Sulfuric Acid on 3. Diazepam. Crude 3 (502 mg) in 25 mL of methanol was treated with 1.0 mL of 100% sulfuric acid and heated to reflux for 3.25 h. Most of the methanol was removed under diminished pressure, and the residue was taken into a mixture of 25 mL of water and an equal quantity of ether. The layers were separated, the ether layer was washed three times with 3% hydrochloric acid, and the combined aqueous acid layers were made basic with ammonia and extracted four times with methylene chloride. The extracts were washed with a small amount of water, filtered through anhydrous sodium sulfate, and concentrated to give 264 mg of pale yellow glass. This residue was taken into about 2–3 mL of alcohol and treated with 60% perchloric acid until acid to congo red. Crystallization of the sparingly soluble **diazepam perchlorate** begins almost at once. It was collected and washed with alcohol: 224 mg, mp 289–291 °C dec (uncor). A small sample was recrystallized from alcohol; mp 289–291 °C dec.

Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_5$: C, 49.89; H, 3.66; N, 7.27. Found: C, 50.01; H, 3.59; N, 7.32.

The ether raffinate, on being dried and concentrated, gave a residue of 160 mg of bright yellow glass which crystallized partially. This material was combined with the material (71 mg) obtained by distributing the mother liquor from the crystallization of the perchlorate between methylene chloride and dilute ammonia and heated to reflux for 3 h with 10 mL of methanol and 0.4 mL of 100% sulfuric acid. By processing this further methanolysis as above, an additional 31 mg of diazepam perchlorate [mp 284–287 °C dec (uncor)] was obtained for a total yield of 255 mg (52.5%).

The ether raffinate from this methanolysis yielded, on thick-layer chromatography, 74 mg of yellow crystalline material (mp

(17) P. Linscheid and J.-M. Lehn, *Bull, Soc. Chim. Fr.*, 992 (1967).

86–93 °C) which on recrystallization from cyclohexane yielded 64 mg (21%) of **5-chloro-2-(methylamino)benzophenone**, mp 94–95.5 °C. From the same thick-layer plate, 21 mg of crude **methyl 5-chloro-2-(methylamino)hippurate** was obtained which after two crystallizations from methanol gave 6 mg of compound with a melting point of 120–122 °C (see below for characterization).

The 255 mg of perchlorate from above was converted to diazepam by distributing the perchlorate between methylene chloride and dilute ammonia (three extractions with methylene chloride). The washed, filtered, and concentrated organic solution on concentration yielded 191 mg of very pale yellow glass which crystallized readily; mp 130–131.5 °C. Recovery from the perchlorate is quantitative. Its mixture melting point with an authentic sample of diazepam was not depressed, its infrared spectrum was indistinguishable from that of authentic diazepam, and its NMR spectrum shows the very characteristic splitting of the methylene protons observed by Lehn.[17]

A further small quantity (11 mg, mp 120–121 °C) of methyl 5-chloro-2-(methylamino)hippurate was obtained from the filtrate of the second crop of the diazepam perchlorate for a total yield of 17 mg (5%).

Action of Phenylmagnesium Bromide on the Trifluoroacetyl Analogue of 2. Freshly prepared trifluoroacetyl derivative (801 mg, mp 176–178 °C, softening from about 170 °C) in 30 mL of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was treated dropwise with stirring at room temperature with 4.6 mL of 1.31 N phenylmagnesium bromide in tetrahydrofuran. A transient red color is produced with each drop; this amount of Grignard solution is enough to give ultimately a red color persisting for 5 min. The solution was then treated with dilute aqueous ammonium chloride and concentrated under diminished pressure to remove most of the tetrahydrofuran.

The residue was diluted with ether, and the ether layer washed with saturated sodium chloride, filtered through anhydrous sodium sulfate, and concentrated to give a yellow glass, 843 mg. Its thin-layer chromatogram showed, in addition to a number of minor spots, two major spots at R_f 0.63 and 0.47; that at R_f 0.63 larger. The R_f of both **2** and its trifluoroacetyl derivative are the same as the spot at R_f 0.47. Integration of the NMR spectrum of this residue suggests that it contains about 44% of **2** or **2** and its trifluoroacetyl derivative; its IR spectrum shows carbonyl absorption at 5.80 μm inter alia.

Acid hydrolysis of this residue (843 mg) in 5 mL of methanol and 0.1 mL of concentrated sulfuric acid with refluxing for 2 h was incomplete as shown by separation into acid-soluble (269 mg) and acid-insoluble (484 mg) fractions as above. The NMR spectrum of the acid-insoluble fraction still showed the presence of substantial amounts of the trifluoroacetyl analogue of **2**. Two similar successive acid hydrolyses with separation into acid-soluble and acid-insoluble fractions yielded 149 and 79 mg more of acid-soluble material acid-insoluble fractions yielded 149 and 79 mg more of acid-soluble material for a total of 497 mg. Its TLC showed a large diazepam spot and, in addition, a bright blue fluorescent spot at R_f 0.68 (methyl 5-chloro-2-(methylamino)-hippurate).

This material was taken into alcohol and treated with 60% perchloric acid dropwise until the solution was acid to congo red.

The crystalline diazepam perchlorate was collected after 4 h in an ice box and washed with alcohol. Air-dried, it weighed 340 mg (29.5%); mp 284–287 °C dec.

The filtrate was concentrated to a small volume at diminished pressure, diluted with methylene chloride, washed with dilute ammonia, filtered through anhydrous sodium sulfate, and concentrated to give 230 mg of yellow glass which crystallized spontaneously; mp 96–110 °C. Two crystallizations from methanol gave 90 mg of product: mp 121–123.5 °C; fine colorless needles; mass spectrum, *m/e* 256, 195, 168, 139, 125, 111, 105, 77, inter alia. Its NMR [δ 6.6 (br s, 1 H), 4.1 (d, 2 H), 3.75 (s, 1 H), 2.8 (s, 3 H)] strongly suggests that its structure is that of methyl 5-chloro-2-(methylamino)hippurate. Its IR shows NH bonds at 2.91 and 3.85 μm, an ester carbonyl at 5.80 μm, and an amide carbonyl absorption at 6.09 μm. This substance presumably arises by the action of methanolic acid on **2**. Its identity was confirmed by its preparation from 5-chloro-2-(methylamino)hippuric acid by the action of diazomethane as follows. 5-Chloro-2-(methyl-amino)hippuric acid (153 mg) suspended in 10 mL of ether was treated with an ethereal diazomethane solution prepared from 1 g of nitrosomethyl urea, 3 mL of 40% potassium hydroxide, and 10 mL of ether. The solid gradually went into solution with gas evolution. The excess diazomethane was destroyed with a few drops of acetic acid, and the solution was washed with dilute sodium carbonate and then with brine, filtered through anhydrous sodium sulfate, and concentrated. The residue, after two crystallizations from methanol, gave 95% mg of methyl 5-chloro-2-(methylamino)hippurate, mp 122–123.5 °C. Its mixed mixture melting point with the material described above was 123–123.5 °C.

Anal. Calcd for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; N, 10.92. Found: C, 51.20; H, 4.89; N, 10.92.