fluorenone (TENF) to which is attached, by a very apt ketone exchange, an optically active aminooxypropionic acid side chain.

The present work deals with an alternative synthesis and resolution of the acid used to introduce the side chain. Advantage is taken of the greater ease of purification of the ethyl ester of the acid. The yield obtained more than compensates for the losses in the added step required to hydrolyze the ester. The proposed resolution permits the isolation of the (−)-ephedrine (−)-acid in addition to the previously characterized diastereoisomer, (−)-ephedrine (+)-acid, in equal yield and in a somewhat purer state.

Experimental

dl-**Ethyl α-(Isopropylidenaminooxy)propionate.**—To 17.5 g. (0.75 mole) of sodium dissolved in 500 ml. of commercial absolute alcohol was added 55 g. (0.75 mole) of acetone oxime. With cooling, 136 g. (0.75 mole) of ethyl α-bromopropionate was added at such a rate that the temperature of the reaction was held at 10–20°. After standing overnight at ambient temperature, the sodium bromide was removed by filtration, and the bulk of the ethanol was removed by distillation. To the residue 250 ml. of water was added, the resulting oil was separated, and the aqueous phase was extracted with ether. The combined oil and ether extract was dried and distilled to give 77 g. (59%) of the ester, b.p. 71.5–73.5° (4–5 mm.). For analysis, redistillation gave a product, b.p. 72–73° (4–5 mm.).

Anal. Calcd. for $C_8H_{15}NO_3$: N, 8.09. Found: N, 8.04, 8.07.

dl-**α-(Isopropylidenaminooxy)propionic acid.**—The above ester (52 g., 0.3 mole) was hydrolyzed in 300 ml. of 5% aqueous sodium hydroxide (0.37 mole) by warming and stirring at 70° for about 30 min. or until the oily globules of the ester had completely disappeared. The solution was cooled and acidified; 175 g. of ammonium sulfate was added. The oil which separated was extracted with ether, the ether solution was dried, the ether was removed by distillation, and 160 ml. of petroleum ether was added to the cooled residue. After refrigeration there was obtained 37 g. (85%) of colorless crystals, m.p. 59–60.5°.

(−)-**Ephedrine (+)-α-(Isopropylidenaminooxy)propionic Acid.**—The *dl* acid (29 g., 0.2 mole) and 35 g. (0.2 mole) of hydrated *l*-ephedrine were dissolved in 800 ml. of a solution made by diluting 48 ml. of commercial absolute alcohol to 800 ml. with ethyl acetate. The solution was cooled, seed crystals were added if available, and crystallization was allowed to proceed for 8–16 hr. in the refrigerator.

The mass of white crystals was filtered with suction and recrystallized from 10 vol. of ethyl acetate without addition of ethanol, using Eastman ethyl acetate (99%). A yield of 22–25 g. (70–80%) melting at 116–119° should be obtained. However, since the yield and its concomitant purity may vary with the impurities present in different brands or batches of solvent, another crystallization or even a change in the amount of ethyl acetate (containing ethanol) may be needed to bring the yield to within the indicated range. In this range both diastereoisomers were isolated with the desired purity.

(−)-**Ephedrine (−)-α-(Isopropylidenaminooxy)propionic Acid.**—The original ethyl acetate filtrate was combined with the filtrate from recrystallization and an amount of pentane equal to the total was added; the solution was kept in the cold for 8–16 hr. The crystals which formed were filtered and air dried to give 26 g. (80%) of the (−)-base (−)-acid monohydrate melting at 88–90°. It was recrystallized from 10 vol. of pure ethyl acetate. On standing over phosphorus pentoxide, the anhydrous salt resulted, m.p. 109–110°, $[\alpha]^{26}D$ −19.1 ± 0.3°.

Anal. Calcd. for $C_{16}H_{28}N_2O_5$: N, 8.53; H_2O, 5.49. Found: N, 8.79, 8.63; H_2O, 5.515.

(+)- **and** (−)-**(Isopropylidenaminooxy)propionic Acid.**—The (−)-base (+)-acid (20 g., 0.064 mole) was dissolved in 60 ml. of water and 14 ml. (0.07 mole) of 5 *N* hydrochloric acid was added. The solution was filtered from a small residue and extracted with ether. The ether solution was dried and the ether was evaporated. Petroleum ether (75 ml.) was added, and the solution was refrigerated overnight. The colorless crystals of the free acid weighed 7.5 g., m.p. 75–81°. The crude product was recrystallized by dissolution in 0.5 vol. of hot acetone and addition of 5 vol. of hexane. After refrigeration, 6.5 g. (70%) of the (+)-acid resulted, m.p. 83–85°.

In a similar manner the (−)-acid resulted from the (−)-base (−)-acid. In this case a melting point of 83–85° was obtained without recrystallization.

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Quinazolines and 1,4-Benzodiazepines. XXIII.[1] Chromic Acid Oxidation of 1,4-Benzodiazepine Derivatives

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In a previous publication,[2] it was shown that 1,3,4,5-tetrahydro-5-nitrophenyl-2H-1,4-benzodiazepin-2-ones could be oxidized with chromium trioxide in glacial acetic acid to the corresponding 1,3-dihydro derivatives. As an extension of this work, we have examined the oxidation of other types of 2,3-dihydro- and 1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepine derivatives, and have utilized the results of these reactions to develop two alternate routes to 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones (VII). Various methods for the preparation of these compounds have appeared previously in the literature[3a-e] and all use as the starting material a 2-aminobenzophenone derivative. In the syntheses discussed below, however, 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones were prepared from either a 2-aminobenzhydrylamine, a 2-aminobenzhydrol, or a substituted 2-halobenzophenone.

Starting with the 2-aminobenzhydrylamine Ia, or the 2-aminobenzhydrol IVa, we were able to synthesize, as shown in Scheme I, the N-substituted amino acid ester IIa. Hydrolysis of this ester to the acid IIIa and subsequent cyclization in xylene yielded the 1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one VIa. This tetrahydro compound was then oxidized by one of several methods to the corresponding 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one VIIa. The oxidation of VIa and related compounds by the use of oxidants such as chromium trioxide, selenium dioxide, or silver oxide leads to the introduction of the 4,5-azomethine bond, and the formation of the desired products of type VII, in yields of up to 80% (Table I). We found, however, that we were unable to oxidize 1-alkyl substituted 1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzo-

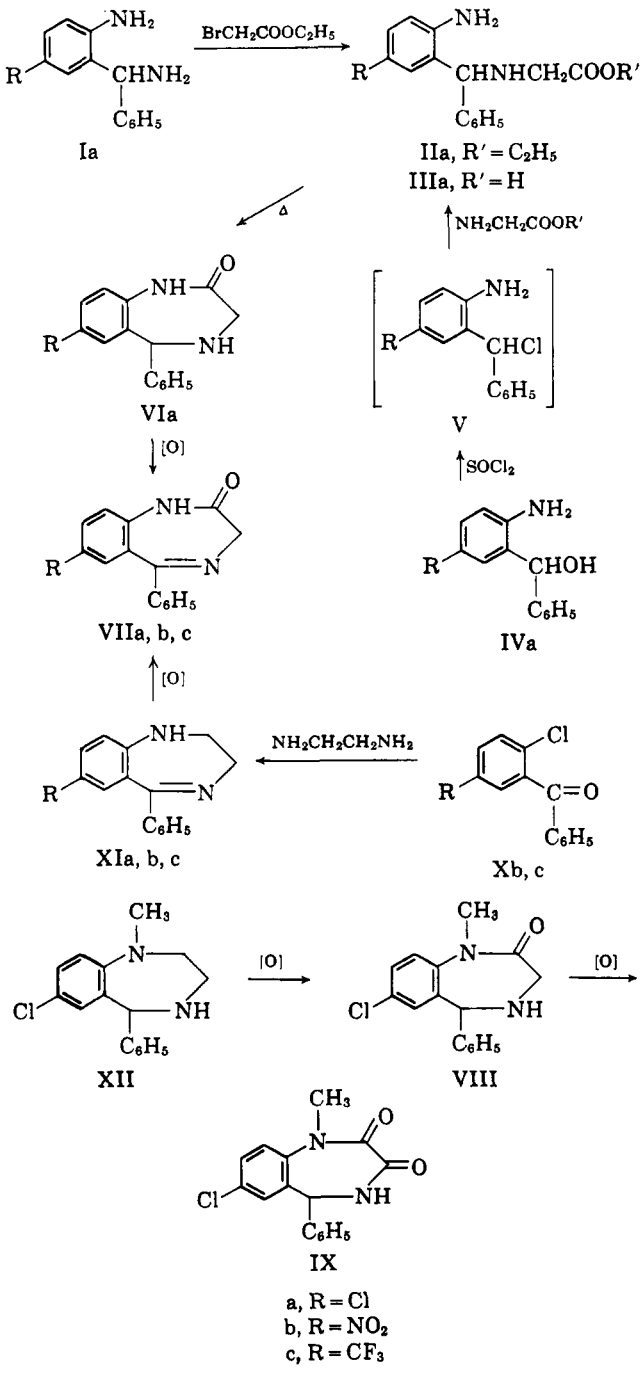
(1) Paper XXII: R. I. Fryer and L. H. Sternbach, *J. Org. Chem.*, **30**, 524 (1965).

(2) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *ibid.*, **30**, 521 (1965).

(3) (a) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961); (b) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962); (c) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962); (d) G. N. Walker, *ibid.*, **27**, 1929 (1962); (e) A. Stempel and F. W. Landgraf, *ibid.*, **27**, 4675 (1962).

diazepin-2-ones to the corresponding 1,3-dihydro derivatives by any of these methods. The only product which could be isolated when VIII was oxidized with chromium trioxide was the known dicarbonyl compound IX.[4] Attempts to oxidize other 1-alkyl analogs of 1,-3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-ones were also singularly unsuccessful and only starting materials were recovered.

SCHEME I



The synthesis of 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepines of type XI, by the reaction between ethylenediamine and an activated *o*-halobenzophenone (Xb, c), has been reported previously,[5,6] and the oxidation of these compounds to the corresponding 2-one derivatives constitutes the second new method for the preparation of compounds of type VII. Literature reports describing the oxidation of secondary and tertiary amines to amides, using either potassium permanganate,[7,8] manganese dioxide,[9] or mercuric acetate,[10] led us to investigate the oxidation of several 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepines. By combining a glacial acetic acid solution of the benzodiazepine with the calculated amount of chromium trioxide in dilute sulfuric acid, we were able to obtain the corresponding 2-one compounds in yields of up to 24% (Table I).[11]

The oxidation of 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine,[12] the 1-methyl derivative of XIa, gave the corresponding 2-one derivative. However in analogy to the 1-alkyl-1,3,4,5-tetrahydro compounds of type VIII discussed above, the oxidation of 1-alkyl-2,3,4,5-tetrahydro-5-phenyl-1H-1,4-benzodiazepines (*e.g.*, XII) led only to the introduction of the amide function (*e.g.*, VIII), and not the azomethine bond.

Experimental

All melting points are corrected. The infrared absorption spectra of starting materials and products were compared whenever necessary, in order to establish structural changes. Identity of compounds was proved by mixture melting point determination and by comparison of infrared spectra. The spectra were determined in 1–5% chloroform solution or in potassium bromide pellets. Where oxidation experiments are repetitive (Table I) only one representative example is given.

Ethyl 2-[1-(2-Amino-5-chlorophenyl)-1-phenylmethylamino]-acetate (IIa). A. From 2-Amino-5-chlorobenzhydrylamine (Ia).—A solution of 30.6 g. of 2-amino-5-chlorobenzhydrylamine dihydrochloride[4] in 150 ml. of water was made basic with a 20% sodium hydroxide solution and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated *in vacuo* to give 2-amino-5-chlorobenzhydrylamine as a pale yellow viscous oil (20.9 g., 90%).

A solution of 11.64 g. of 2-amino-5-chlorobenzhydrylamine and 7.2 ml. of triethylamine in 100 ml. of anhydrous benzene was stirred in an ice bath at 0–5° and treated dropwise during 20–30 min. with a solution of 5.52 ml. of ethyl bromoacetate in 20 ml. of dry benzene. The mixture was stirred for 16 hr. at 25° and was finally heated under reflux for 1 hr. on the steam bath. After cooling, the reaction mixture was poured into water and extracted with dichloromethane to give the crude product as a bright yellow oil (14.09 g.). This was partitioned between dilute hydrochloric acid and ether; the aqueous acid layer was made basic with sodium hydroxide solution and extracted with dichloromethane to give the basic fraction as a yellow gum (10.75 g.). Trituration with hexane and several recrystallizations from hexane and finally from ethanol gave 2.5 g. (16%) of IIa as colorless rods, m.p. 103–104°.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2$: C, 64.04; H, 6.00; N, 8.79. Found: C, 64.20; H, 5.95; N, 8.75.

B. From 2-Amino-5-chlorobenzhydrol (IVa).—A solution of 5.66 g. of 2-amino-5-chlorobenzhydrol[3d] in 80 ml. of ethylene dichloride was treated with dry hydrogen chloride, which was bubbled through the solution until an excess was present, and then with 3.48 ml. of thionyl chloride. Pyridine (2 drops) was added and the mixture was stirred and refluxed for 0.5 hr. with protection from atmospheric moisture. Solvents were then evaporated *in vacuo*. The residue was dissolved in 60 ml. of

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(5) J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961).
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(9) E. F. Pratt and T. P. McGovern, *J. Org. Chem.*, **29**, 1540 (1964).
(10) N. J. Leonard and W. K. Musker, *J. Am. Chem. Soc.*, **82**, 5148 (1960).
(11) Oxidation of XIb using the permanganate method of Forrest, Liddell, and Tucker,[7] gave only a 4.5% yield of VIIb.
(12) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

dichloromethane, cooled in an ice bath, and treated dropwise during 0.5 hr. with a solution of 10.3 g. of freshly distilled glycine ethyl ester in 25 ml. of dichloromethane. The mixture was stirred for 1 hr. at 25° and was then poured into water. Isolation of the product, as described above, gave IIa (2.47 g., 32%), identical with the sample prepared by method A.

2-[1-(2-Amino-5-chlorophenyl)-1-phenylmethylamino]acetic Acid (IIIa).—A mixture of 1.81 g. of IIa, 30 ml. of saturated methanolic barium hydroxide solution (*ca.* 1 *N*), and 10 ml. of water was heated under reflux for 17 hr. The barium salt of IIIa which crystallized on cooling the mixture was obtained by filtration. Recrystallization from water gave 1.73 g. (42%) of the salt as colorless needles, m.p. 206–210°, undepressed on admixture with an authentic sample,[13] m.p. 207–208°. For positive identification, the barium salt was converted to the free acid IIIa by treatment with dilute sulfuric acid as previously described,[3a] and also to the known methyl ester[3a]; both products were identical with authentic samples.

7-Chloro-1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VIa).—A suspension of 1 g. of IIIa in 20 ml. of xylene was stirred and heated under reflux using a Dean–Stark head until no more water separated (6 hr.). The mixture was cooled and filtered, giving 0.76 g. (81%) of VIa as colorless prisms, m.p. 181–185°, undepressed on admixture with an authentic sample.[3a]

Oxidation of VIa to 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VIIa). A. Chromium Trioxide in Acetic Acid.—A solution of 2.0 g. (0.02 mole) of chromium trioxide in a small amount of water was added to a solution of 5.45 g. (0.02 mole) of VIa[3a] in 50 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature for 12 hr., diluted with ice–water, and made basic (pH 8) with ammonium hydroxide. The precipitate was filtered and dissolved in dichloromethane. The dichloromethane solution was washed with water, dried, and concentrated. Recrystallization of the residue from acetone gave 1.35 g. of VIIa,[3a] m.p. and m.m.p. 215–217° with an authentic sample.

B. Selenium Dioxide.—A mixture of 1.28 g. (4.7 mmoles) of VIa, 1.0 g. (9.0 mmoles) of selenium dioxide, 1.4 ml. of pyridine, and 100 ml. of *t*-butyl alcohol was heated at 60° for 30 min. The mixture was cooled and filtered through Celite. Evaporation of solvents gave a pink residue which was recrystallized from methanol to give 0.9 g. of VIIa, m.p. 213–215°.

C. Silver Oxide.—A suspension of 1.43 g. (5.26 mmoles) of VIa in a solution of 1.8 g. (10.52 mmoles) of silver nitrate in 0.4 ml. of ethanol and 4.0 ml. of water was treated with a solution of 0.8 g. (20 mmoles) of sodium hydroxide in 5.6 ml. of water. The mixture was shaken at room temperature for 18 hr. The solids were removed by filtration and washed with dichloromethane. The filtrate was acidified with dilute sulfuric acid and extracted with dichloromethane. All organic fractions were combined, washed with water, dried, and concentrated. Recrystallization of the residue from methanol gave 1.2 g. of VIIa, m.p. 210–215°.

The Oxidation of 2,3-Dihydro-7-nitro-5-phenyl-1H-1,4-benzodiazepine (XIb) to 1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (VIIb). A. Chromium Trioxide and Dilute Sulfuric Acid in Acetone.—A solution of 1.0 g. (3.75 mmoles) of XIb[6] in 250 ml. of purified acetone[14] was treated under an atmosphere of dry nitrogen with 0.936 ml. (2.50 mmoles) of chromate reagent.[14] The mixture was heated and allowed to reflux for 1 hr. and then poured into 1.5 l. of cold water. The products were extracted into dichloromethane, which was washed, dried, and concentrated. Recrystallization of the residue from methanol gave a first crop of 0.75 g. of prisms, m.p. 211–212°, shown by mixture melting point to be identical with starting material. A second crop of prisms, m.p. 175–210°, was treated with ether and the ether-soluble portion was crystallized to yield 25 mg. of pure VIIb, m.p. and m.m.p. 223–228° with an authentic sample.[15]

TABLE I

Reactant	Oxidant	Solvent[a]	Time, hr.	Temp., °C.	Product	Yield, %
XII	CrO_3–H_2SO_4	A	0.1	23	VIII	15.4
VIa	CrO_3	B	12	23	VIIa	25
	SeO_2	C–D	0.5	60–70	VIIa	70
	Ag_2O	E	18	23	VIIa	84
XIa	CrO_3–H_2SO_4	A	3	56	VIIa	17.3
XIb	$KMnO_4$	A–D	1	56	VIIb	4.5[b]
	CrO_3–H_2SO_4	A	1	56	VIIb	2.4
	CrO_3–H_2SO_4	B	18	22	VIIb	14.3
	CrO_3–H_2SO_4	B	0.5	22	VIIb	24
XIc	CrO_3–H_2SO_4	B	0.5	22	VIIc	20

[a] A = acetone; B = acetic acid; C = 1-butanol; D = pyridine; and E = dilute ethanol. [b] See ref. 7.

B. Chromium Trioxide and Sulfuric Acid in Glacial Acetic Acid.—A solution of 1.0 g. (3.75 mmoles) of XIb in 15 ml. of glacial acetic acid was treated at room temperature with 0.936 ml. (2.5 mmoles) of chromate reagent[14] and stirred for 30 min. The mixture was poured into 800 ml. of water, made basic with ammonium hydroxide, and extracted with dichloromethane. The organic layers were combined, washed, dried, and filtered through 10 g. of Woelm Grade I neutral alumina. Eluting the alumina with dichloromethane gave, after recrystallization from methanol, 0.625 g. of starting material (62.5%), m.p. 210–212°. Washing the alumina with methanol and recrystallizing the residue obtained after removal of solvent gave 0.25 g. of VIIb (23.8%), m.p. 221–225°.

The Oxidation of 7-Chloro-2,3,4,5-Tetrahydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (XII) to 7-Chloro-1,3,4,5-tetrahydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.—A solution of 0.836 g. (3.06 mmoles) of XII[12] in 100 ml. of purified acetone[14] was treated with 0.76 ml. (2.04 mmoles) of chromate reagent[14] and stirred at room temperature for 1 hr. The reaction mixture was diluted to 1.5 l. with water, made basic (pH 8) with ammonium hydroxide, and extracted with dichloromethane (three 50-ml. portions). The organic layers were combined, washed, dried, and evaporated to give 0.55 g. of an oil. Crystallization and recrystallization from ether–petroleum ether gave 140 mg. (16%) of pure VIII, m.p. and m.m.p. 142–144° with an authentic sample[16].

The Oxidation of VIII to 7-Chloro-1-methyl-5-phenyl-4,5-dihydro-2H-1,4-benzodiazepin-2,3-(1H)-dione (IX).—A solution of 2.5 g. (8.4 mmoles) of VIII[16] in 200 ml. of purified acetone[14] was treated with 2.44 ml. (6.5 mmoles) of chromate reagent[14] and heated under reflux for 3.5 hr. The reaction mixture was cooled and filtered through Celite. The filtrate was diluted with 1 l. of water, made basic (pH 8) with ammonium hydroxide, and extracted with dichloromethane (three 50-ml. portions). The organic layers were combined, washed, dried, and evaporated to give 1.5 g. of a colorless oil. Crystallization and recrystallization from acetone–hexane gave 0.12 g. (6.7%) of pure IX, m.p. and m.m.p. 228–230° with an authentic sample[4].

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Mr. S. Traiman and his co-workers for the infrared spectra.

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(14) See C. Djerassi, *et al.* [*ibid.*, **21**, 1547 (1956)], for the purification of acetone and preparation of the chromate reagent.

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