TABLE I

RADIATION-CATALYZED OXALYL CHLORIDE–ETHYLENE TELOMERIZATION AT 25°

Run no.[a]	$[(COCl)_2]_0/[C_2H_4]_0$ (mole ratio)[b]	Telomer yield (mole % on telogen) 1:1	2:1	3:1	G (telomers)[c]	C_n[d] $n = 1$ (k_2/k_4)	$n = 2$	$n = 3$
1	0.59	0.60	4.68	0.06	500	0.21 (0.22)	~120	~6
2	0.60	..	...	...	~100	.. (0.21)[e]	...	...
3	1.1	2.9	10.2	0.08	1400	0.26 (0.26)	~110	~7
4	1.1	...	...	...	~50	..	...	...
5[f]	1.1	2.1	8.60	0.07	220	0.22 (0.22)	~110	~7
6[g]	1.1	0	0	0	0	..	...	...
7	1.9	4.2	9.55	0.02	1500	0.23 (0.23)	~180	~0.3
8	1.9	...	...	...	~50	..	...	...

[a] Dose rate in each run = 1.5×10^4 rep (in water); dosage = 0.63 M rep except in runs 5 (3.2 M rep) and 6 (2.4 M rep). [b] For liquid phase. [c] Based on uncorrected radiation dosages. [d] See ref. 4 for formula. [e] Only 1:1–2:1 yield ratio was determined. [f] Recovered 0.99 mole of carbon monoxide/mole of telomers. [g] Starting mixture contained 1 mole % oxygen.

b.p. 63–64° (4 mm.), lit.[12] b.p. 56–58° (2.5 mm.), neut. equiv. 77.5 (calcd. 77.5), and likewise 7-chloroheptanoyl chloride, b.p. 82° (2 mm.), neut. equiv. 91.0 (calcd. 91.5). Reaction of the acid chlorides with ethanol gave, after distillation, 99+ wt. % pure samples of ethyl 5-chloropentanoate, b.p. 83.5–84.5° (8 mm.), $n^{25}D$ 1.4339, lit.[13] b.p. 83.5–85° (8 mm.), $n^{20}D$ 1.4355, and ethyl 7-chloroheptanoate, b.p. 91.5° (2 mm.), $n^{25}D$ 1.4391.

(12) N. Clark and A. Hams, *J. Biochem.*, **55**, 839 (1953).

(13) L. Cheney and J. R. Piening, *J. Am. Chem. Soc.*, **67**, 731 (1947).

The Isolation of a Cyclic Intermediate in the Ketone–Alkoxyacetylene Reaction

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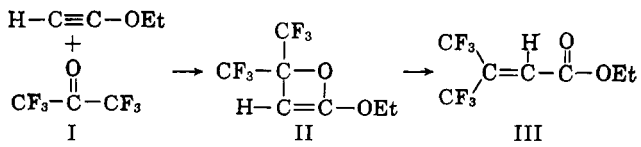
Ketones react with alkoxyacetylenes in the presence of boron trifluoride catalyst to give α,β-unsaturated esters in high yield.[1] The formation of an oxete as a cyclic intermediate has been postulated for this reaction,[1] but such an intermediate has not been isolated previously.

We have found that hexafluoroacetone (I) reacts vigorously and exothermically with ethoxyacetylene without added catalyst. When the reaction is conducted at room temperature, ethyl β,β-bis(trifluoromethyl)acrylate (III) is formed. If the reaction is carried out at lower temperatures, however, the intermediate oxete II can be isolated and characterized. This oxete II slowly isomerizes to the ester III if stored at room temperature for a few days. This rearrangement is exothermic and becomes rapid at about 70°.



Experimental[2]

2-Ethoxy-4,4-bis(trifluoromethyl)-2-oxete.—Hexafluoroacetone, 10.5 ml. measured at −78° (0.1 mole), was slowly distilled into a flask that contained 7.0 g. (0.1 mole) of freshly distilled ethoxyacetylene precooled to −78°. Strong cooling was maintained during the entire addition. The dark reaction mixture was distilled at reduced pressure to give 20.1 g. (85% yield) of 2-ethoxy-4,4-bis(trifluoromethyl)-2-oxete as a colorless oil, b.p. 29–30° (8 mm.), $n^{25}D$ 1.3331. The F^{19} n.m.r. spectrum showed a singlet at 10.7 p.p.m., and the proton n.m.r. spectrum showed a singlet at 4.60 p.p.m. in addition to resonance lines attributed to the ethyl group. The infrared spectra contained a band at 5.93 for C=C and at 3.14 μ for =CH.

Anal. Calcd. for $C_7H_6F_6O$: C, 35.61; H, 2.57; F, 48.28. Found: C, 35.41; H, 2.87; F, 48.22.

Ethyl β,β-Bis(trifluoromethyl)acrylate.—A sample of 2-ethoxy-4,4-bis(trifluoromethyl)-2-oxete that had been stored at room temperature for 2 weeks was found to have isomerized quantitatively to ethyl β,β-bis(trifluoromethyl)acrylate, b.p. 126–127°, $n^{25}D$ 1.3382.[3] The infrared spectrum of this ester contained bands at 5.96 (C=C) and 5.72 μ (C=O). The F^{19} n.m.r. spectrum showed two quartets (J = 8 c.p.s.) centered at −4.61 and −0.18 p.p.m. The proton n.m.r. spectrum contained a singlet at 7.22 p.p.m. in addition to resonance lines attributed to the ethyl group.

Anal. Calcd. for $C_7H_6F_6O_2$: C, 35.61; H, 2.57; F, 48.28. Found: C, 34.45; H, 2.73; F, 48.07.

(1) H. Vieregge, H. J. T. Bos, and J. F. Arens, *Rec. trav. chim.*, **78**, 664 (1959).

(2) Fluorine n.m.r. spectra were obtained with a Varian Associates high-resolution n.m.r. spectrometer operating at 56.4 Mc./sec. Spectra were calibrated in terms of higher field displacement in p.p.m. from the F^{19} resonance of 1,2-difluorotetrachloroethane used as an external reference. Proton resonance spectra were obtained with a Varian Associates A-60 spectrometer. Spectra were calibrated in terms of lower field displacement in p.p.m. from the proton resonance of tetramethylsilane used as an internal reference.

(3) I. L. Knunyants and Yu. A. Cherburkov [*Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2162 (1960)] report b.p. 128° (747 mm.) and $n^{20}D$ 1.3414 for this compound, which was prepared by the esterification of the corresponding acid.

(+)- and (−)-(Isopropylidenaminooxy)-propionic Acid

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In 1955 Newman and Lutz[1] introduced optically active α-(2,4,5,7-tetranitro-9-fluorenylidenaminooxy)-propionic acid, subsequently abbreviated TAPA,[2] for the resolution of polycyclic aromatic hydrocarbons which do not possess a functional group capable of salt formation with an optically active acid or base. This compound consists of the complexing agent, tetranitro-

(1) M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).

(2) M. S. Newman and D. Lednicer, *ibid.*, **78**, 4765 (1956).

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).