Structure Related to Morphine. XXVI.[1] Cyclization Experiments with 2-Benzyl-1,3,4-trialkyl-1,2,5,6-tetrahydropyridines. Improved Yields of β-5,9-Dialkyl-6,7-benzomorphans

J. HARRISON AGER, S. E. FULLERTON, E. M. FRY, AND
EVERETTE L. MAY

*Laboratory of Chemistry, National Institute of Arthritis and
Metabolic Diseases, National Institutes of Health,
Bethesda 14, Maryland*

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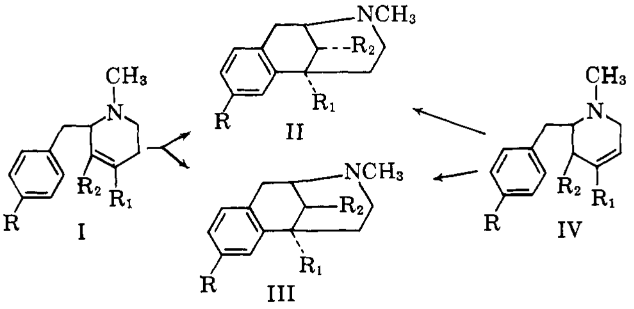
Previously[1-4] we reported that cyclization of 3,4-dialkyl-2-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridines (I) with 48% hydrobromic acid at 130–150° affords a mixture of diastereoisomeric 6,7-benzomorphans (II and III) in a ratio of about 10:1. Because the lesser isomers (III) (designated β)[5] are many times more potent as neuropharmacologic agents than α compounds (II) or morphine and not commensurately more toxic,[1] we wish to record improvements in the yields of IIIa, IIIc, and IIIe along with failures of I to undergo cyclization when R_1 = H.



a, R = H, $R_1 = R_2 = CH_3$
b, R = MeO, $R_1 = R_2 = CH_3$
c, R = HO, $R_1 = R_2 = CH_3$
d, R = MeO, $R_1 = R_2 = C_2H_5$
e, R = HO, $R_1 = R_2 = C_2H_5$
f, R = MeO, $R_1 = R_2$ = H
g, R = MeO, R_1 = H, $R_2 = CH_3$

A marked increase (*cf.* Table I) in the yield and proportion of IIIc and IIIe was noted with 85% phosphoric acid; optimal temperature (bath) and time were 180–185° and 40–45 hours, respectively. Although aluminum bromide or aluminum chloride and I in carbon disulfide gave nothing but tarry material when the hydrobromide or hydrochloride salt of I was used, cyclization proceeded smoothly and in good yield. In the case of Ia hydrobromide, surprisingly, IIIa (β) was formed in 42–44% yield and in marked predominance over the usually predominant α isomer. On the other hand when R_1 was methoxy (Ib and Id), the stereochemistry of cyclization was not materially different from that seen with 85% phosphoric acid. Between these two extremes but closer to Ia than to Ib and Id were the phenolic compounds Ic and Ie which, as the hydrochloride salts, were converted to IIIc and IIIe in yields of 17 and 35% and in II:III ratios of 3.5:1 and 1:2, respectively. Thus, based on these limited data, the *p*-substituent of I favors III formation in the sequence H > OH > OCH_3 when aluminum bromide is the cyclizing agent. It is difficult to explain these substituent effects except on the basis of their influence on the speed of cyclization. Groups tending to decelerate reaction apparently favor β-benzomorphan formation. Finally, Fry[6] has observed that cyclization of the Δ^4-isomer (IVa) of Ia with aluminum chloride yields exclusively the β compound IIIa, but with hot hydrobromic acid, principally IIa (*via* Ia) is produced.

TABLE I

CYCLIZATION OF 2-BENZYL-2-METHYL-3,4-DIALKYL-1,2,5,6-TETRAHYDROPYRIDINES

Starting compound	Cyclizing medium	Bath temp., °C.	Yield, % α (II)	Yield, % β (III)	II:III Ratio
Ia	48% HBr^a	150	90^b	6^b	15
Ia	$AlBr_3(CS_2)^{c,d}$	25^e	15	45^d	0.3
Ib	48% HBr^a	140–150	$76^{f,b}$	7^f	11
Ib	85% $H_3PO_4{}^g$	140–150	56	7.5	7.3
Ib	85% H_3PO_4	180–185	50	9	5.5
Ib·HBr	$AlBr_3(CS_2)$	25	65	10	6.5
Ic·HCl	$AlBr_3(CS_2)$	Reflux	57	17	3.4
Id	48% HBr	140–145	75^h	6.6^h	11.3
Id	85% H_3PO_4	180–185	54	13.5	4
Id·HCl	$AlBr_3$	25	45	12	3.8
Ie·HCl	$AlBr_3$	Reflux	20	39	0.5

[a] Reaction time, 20–25 hr. [b] Ref. 10. [c] Aluminum chloride serves equally well although in this instance reaction is not nearly so exothermic. [d] Ref. 6. [e] Room temperature. When 5–10-g. runs were made the carbon disulfide suspension of I boiled vigorously when aluminum bromide was added. [f] Ref. 4. [g] Reaction time, 44–48 hr. [h] Ref. 3.

The addition of benzoyl peroxide to the hydrobromic acid cyclization mixtures did not increase the yield of III. In general, varying concentrations of sulfuric acid led to *lower* yields of both II and III. Boron trifluoride or boron tribromide, under a variety of conditions, were ineffective in the cyclization of Ib (base). Finally, it is noteworthy that when R_1 was H (*e.g.*, If, Ig) ring closure to corresponding benzomorphans could not be effected by any of the procedures normally used. Starting materials and/or decomposition products were usually obtained. When boiling hydrobromic acid was used hydrogen bromide adducts of If and Ig were produced.

The cyclization products II and III were identified by infrared, melting point, and solubility comparisons with authentic compounds previously prepared in this laboratory. The stereochemistry of compounds IIc and IIIc has already been established[5]; IIa and IIIa have now been confirmed by the same methiodide-rate-study method.[5] Thus IIa was found to react with methyl iodide at least ten times more rapidly than IIIa, whose skeletal structure was proved by degrading it to 1,2-dimethylnaphthalene.[6]

Experimental

Melting points were determined in a capillary with total-immersion thermometers. Microanalyses are by the Analytical Services Unit of this laboratory, Harold McCann, director, and

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[1] Paper XXV, J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

[2] S. E. Fullerton, J. H. Ager, and E. L. May, *J. Org. Chem.*, **27**, 2554 (1962).

[3] J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962).

[4] J. H. Ager and E. L. May, *ibid.*, **24**, 1432 (1959).

[5] S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

[6] E. M. Fry, *ibid.*, **28**, 1869 (1963).

infrared spectra are from H. K. Miller and Mrs. Ann Wright, also of this laboratory.

1,3-Dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine (Ig) Picrate.—1,3-Dimethyl-1,2,5,6-tetrahydropyridine (9 g.),[7] 30 ml. of acetone, and 12.6 g. of *p*-methoxybenzyl chloride[8] were kept at 25-30° for 24 hr. Addition of 30 ml. of dry ether, thorough manual stirring, and decantation left a white dough which was similarly treated with another portion of ether. The residual quaternary compound was dried to constant weight *in vacuo* at a bath temperature of 35° (2-3 hr.). A nearly white, hygroscopic, amorphous powder (14.3 g. 66%) resulted. To 10 g. of this was added rapidly (stirring) 120 ml. of 0.9 *M* ethereal phenyllithium. The mixture was stirred for 2 hr., refluxed for 30 min., poured into ice-water, and the ethereal layer extracted thrice with excess 10% hydrochloric acid. The extracts were made alkaline with aqueous ammonia and the liberated bases dried in ether. Evaporation of the ether and short-path distillation of the residue at 170-180° (0.4 mm., air bath) gave 6.0 g. of crude Ig. This and alcoholic picric acid yielded 5.7 g. of Ig picrate which could be recrystallized from acetone-water; m.p. 113-116°.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.8; H, 5.3; N, 12.2. Found: C, 55.5; H, 5.5; N, 12.1.

The **hydrochloride of Ig**, prisms from alcohol-acetone, melted at 214-215°.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.3. Found: C, 67.3; H, 8.4.

The **methiodide of Ig**, needles from ethanol, had m.p. 213-216° dec.

Anal. Calcd. for $C_{16}H_{24}INO$: C, 51.5; H, 6.5; I, 34.0. Found: C, 51.8; H, 6.8; I, 35.1.

Attempts to cyclize Ig by any of the methods given in Table I were unsuccessful. Boron tribromide or trifluoride also were ineffective. This was true also of If.[9] Starting material or the phenolic counterpart was usually obtained along with hydrogen bromide adducts of the latter. These adducts lost hydrogen bromide on distillation *in vacuo*.

2-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (Ia) Hydrobromide.—The base Ia[6,10] and its picrate[11] have been described. The hydrobromide of Ia, prepared in ether (hydrogen bromide) and recrystallized from acetone, melted at 151-153°.

Anal. Calcd. for $C_{15}H_{22}NBr$: C, 60.8; H, 7.5. Found: C, 61.1; H, 7.4.

2-*p*-Methoxybenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (Ib) Hydrobromide.—Base Ib[10,11] in acetone-ether was treated with hydrogen bromide to give the hydrobromide; needles, m.p. 143-145°.

Anal. Calcd. for $C_{16}H_{24}BrNO$: C, 58.9; H, 7.4. Found: C, 59.0; H, 7.1.

3,4-Diethyl-2-(*p*-methoxybenzyl)-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (Id) Picrate.—The base Id[3,11] with picric acid in acetone gave this picrate as orange crystals, m.p. 127-129°.

Anal. Calcd. for $C_{24}H_{30}N_4O_8$: C, 57.4; H, 6.0; N, 11.2. Found: C, 57.6; H, 5.9; N, 10.9.

The **hydrochloride of Id**, prepared from the picrate with acetone-hydrogen chloride, crystallized from acetone in rectangular prisms of m.p. 165-166°.

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 69.8; H, 9.1. Found: C, 70.0; H, 9.3.

2-(*p*-Hydroxybenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (Ic) Hydrochloride.—The hydrobromide of Ib (2.0 g.) and 11 ml. of 48% hydrobromic acid were refluxed vigorously for 15-20 min., cooled, made alkaline with aqueous ammonia, and extracted with chloroform. Evaporation of the dried extracts left a residue which was dissolved in a few milliliters of acetone. On cooling to 5°, 95 mg. (6%) of IIc separated. The filtrate was acidified to pH 3-4 with hydrogen chloride. Cooled to −15°, 1.1 g. (60%) of Ic hydrochloride, m.p. 206-209°, separated; needles from acetone-methanol.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.3. Found: C, 67.5; H, 8.4.

3,4-Diethyl-2-(*p*-hydroxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (Ie) Hydrochloride.—As described previously, 2.0 g. of Id gave 4% of IIe and 60% of Ie hydrochloride; prisms, m.p. 176-178.5°, from acetone-methanol.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.0; H, 8.9. Found: C, 69.1; H, 8.8.

Cyclization Procedures. A. With Acid.—In general, the procedures used in the cyclization of pure Ia,[10] Ib,[4] and Id[3] with 48% hydrobromic or 85% phosphoric acid were the same as those described before for the unpurified compounds. The results are given in Table I.

B. With Aluminum Bromide and Ia.—To 5 g. of Ia hydrobromide and 20 ml. of carbon disulfide was added during 2-3 min., 5.0 g. of aluminum bromide. The reaction was very exothermic. After a few minutes of swirling, the flask was stoppered and kept at room temperature for 2-3 hr. Carbon disulfide was decanted and ice-water was added to the residue. Addition of ammonium hydroxide and extraction of the liberated base from the gelatinous material with three to four portions of ether gave, after drying and evaporation of the ether, 3.3 g. of oil. This in acetone-ether was acidified with hydrogen bromide to give 2.2 g. (45%) of **IIIa hydrobromide**, m.p. 245-255°; rods from acetone-methanol, m.p. 265-266°.

Anal. Calcd. for $C_{15}H_{21}NBr$: C, 60.8; H, 7.5. Found: C, 60.7; H, 7.7.

From the filtrate of the 2.2 g., 10-15% yield of IIa could be isolated as the picrate, m.p. 113-123°.[10] Aluminum chloride was equally effective in the cyclization of Ia hydrochloride.

C. With Aluminum Bromide and Ib.—Aluminum bromide (1.7 g.) was added during 2-3 min. to 0.8 g. of Ib hydrobromide in 10 ml. of carbon disulfide. The mixture was kept (occasional swirling) at 25-30° for 2 hr., and refluxed 2-3 min. Carbon disulfide was evaporated and the residue was treated slowly (ice cooling and stirring) with 10 ml. of 48% hydrobromic acid. The solution was refluxed for 30 min., cooled, made alkaline with aqueous ammonia, and the gel extracted several times with 3:2 1-butanol-benzene. The extracts were evaporated to thorough dryness *in vacuo*. The residue was triturated with 2-3 ml. of acetone to give, after cooling at −15° overnight, 0.42 g. of solid. This was suspended in 3-5 ml. of methanol and hydrogen chloride added to pH 3-4. Cooling to −5° overnight gave 46 mg. of **IIIb hydrochloride**, m.p. 269-272°.[4,5] Similar treatment of the filtrate from 0.42 g. of previous solid gave an additional 10 mg.; total yield of IIIb hydrochloride, 10%. Treatment of the methanol filtrate from the 46 mg. of IIIb hydrochloride with aqueous ammonia gave 0.36 g. (65%) of IIb.[4,5,10]

D. With Aluminum Bromide and Id.—A mixture of 3.0 g. of Id hydrochloride, 15 ml. of carbon disulfide, and 5.0 g. of aluminum bromide was kept at room temperature in a stoppered flask for 24-72 hr. The solvent was evaporated and the residue treated (gradually at first, ice cooling) with 25 ml. of 48% hydrobromic acid. The solution was refluxed for 2-3 hr., cooled, and made alkaline with aqueous ammonia. The gel was extracted liberally with 3:2 1-butanol-benzene. Drying and evaporation of the extracts to thorough dryness *in vacuo* left 2.1 g. of a residue which crystallized from 8 ml. of acetone (cooling 5-6 hr. at −15°) in a yield of 1.15 g. (45% of IIe)[3,5]; m.p. 240-247°[12]; λ_{max}^{Nujol} 6.15 (m), 6.31 (s) μ.

The filtrate was evaporated to dryness and the residue evaporatively distilled [180-200° (0.1 mm.)]. The distillate was dissolved in acetone and the solution concentrated to 3-5 ml. Prolonged cooling at −15° gave 0.31 g. (12%) of IIIe[3,5]; m.p. 202-209°; λ_{max}^{Nujol} 6.20 (s) μ.

E. Aluminum Bromide with Ic.—A mixture of 1.1 g. of Ic hydrochloride, 3 g. of aluminum bromide, and 7 ml. of carbon disulfide was refluxed for 3-4 hr., evaporated to dryness and treated with ice-aqueous ammonia. The gelatinous mixture was extracted four times with chloroform or 3:2 1-butanol-benzene. Drying and evaporation *in vacuo* of the extracts gave 1 g. of solid which was suspended in 5 ml. of methanol. Hydro-

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[7] M. Ferles who prepared this compound by either sodium borohydride [*Chem. Listy*, **51**, 474 (1957)] or lithium aluminum hydride [*ibid.*, **52**, 668 (1958)] reduction of 1,3-dimethylpyridinium iodide reported a m.p. of 105° for the picrate of this tetrahydropyridine. Our picrate prepared from base obtained in the borohydride procedure melted at 111-112°. The hydrobromide crystallized from ethanol-ether in needles, m.p. 152-154°. *Anal.* Calcd. for $C_7H_{14}BrN$: C, 43.8; H, 7.4; Br, 41.6. Found: C, 43.1; H, 7.3; Br, 41.4.

[8] T. F. Dankova, L. G. Evdokimova, I. I. Stepanow, and N. A. Preobrazhenski, *J. Gen. Chem. USSR* (Eng. Transl.), **18**, 1724 (1948); *Chem. Abstr.*, **43**, 2606 (1949).

[9] Personal communication from S. Saito, former Visiting Fellow from Osaka, Japan.

[10] E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

[11] E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961).

[12] Occasionally this IIe melted at 220-240° due to contamination with IIIe. If so, this fraction (1.3 g.) was digested for 5-10 min. with 20-25 ml. of boiling acetone; the digest was cooled for 6 hr. at −15° and filtered giving 1.1 g. of IIe, m.p. 242-248°. The filtrate then gave 100 mg. of IIIe, m.p. 205-211°, λ_{max}^{Nujol} 6.20 μ, as described previously.

gen chloride was added to a pH 3–4 and the solution seeded with IIIc hydrochloride. On cooling to −15°, 0.19 g. (17%), of pure **IIIc hydrochloride** separated.

The filtrate, made basic with dilute, aqueous ammonia, yielded 0.54 g. (57%) of pure IIc.

F. **Aluminum Bromide and Ie.**—Cyclization of 1.0 g. of Ie hydrochloride was carried out as described for Ic. The residue from evaporation of the butanol–benzene extracts gave from 7 ml. of acetone (−5°), 0.22 g. of IIe, m.p. 240–246°.[12] The filtrate, concentrated to 2–3 ml., seeded with IIIe, and kept for 24–48 hr. at −15°, gave 0.35 g. of nearly pure IIIe; m.p. 198–205°; $\lambda_{\max}^{\text{Nujol}}$ 6.20 (s) μ.

Confirmation of IIa and IIIa Stereochemistry.[5]—Chloroform (20 ml.), 21.0 mg. of IIa, and 0.04 ml. of methyl iodide were left at 25° for 4 hr., and titrated with 0.0204 *N* acetous perchloric acid (Oracet Blue B indicator), 1.6 ml. being required. This corresponds to 33% of starting II or 67% methiodide formation in 4 hr. Similar reaction of 20.1 mg. of IIIa with 0.04 ml. of methyl iodide gave only 6.5% methiodide formation. These results are in accord with those observed for IIc and IIIc and leave no doubt that the orientation of the 9-methyl substituent in IIa and IIIa is as shown.[5]

A Simplified Procedure for the Preparation of Diazocyclopentadiene and Some Related Compounds

THEODOR WEIL[1]

FMC Corporation Chemical Research and Development Center,
Princeton, New Jersey

MICHAEL CAIS

Technion, Israel Institute of Technology, Haifa, Israel

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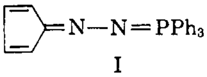
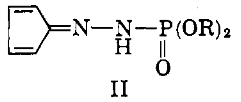
Diazocyclopentadiene previously has been prepared by Doering and DePuy[2] from *p*-toluenesulfonyl azide, cyclopentadiene, and phenyllithium. We have found in the present study that in this reaction phenyllithium can be replaced by almost any base, preferably by diethylamine or ethanolamine. The mixture of the reactants, cyclopentadiene, *p*-toluenesulfonyl azide, and the base, was simply left for some time at 0° and, after addition of water, was extracted with pentane. In view of its explosiveness[3] it seemed preferable not to isolate the diazocyclopentadiene in pure form but to use the pentane extracts directly for further reactions. These solutions were indeed sufficiently pure for most purposes. The diazocyclopentadiene formed was identified, and its yield determined by the isolation of (cyclopentadienylhydrazono)triphenylphosphorane[3] (I), the reaction product with triphenylphosphine.



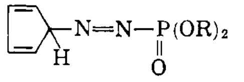
I

The reaction also was extended to diazoindene, which was prepared from indene, diethylamine, and *p*-toluenesulfonyl azide. In this case too, in order to avoid the isolation of the diazo compound itself, we prepared its derivative with triphenylphosphine. Diazofluorene, however, could not be prepared by this method. Both diazofluorene[4] and (fluorenylhydrazono)triphenylphosphorane[5] have been prepared earlier.

Furthermore we found that the reaction of diazocyclopentadiene with dialkyl phosphites yielded a new class of compounds to which we assigned tentatively the structure II or IIa.



II



IIa

Experimental

Diazocyclopentadiene.—A mixture of 20 g. of *p*-toluenesulfonyl azide, 8 ml. of freshly distilled cyclopentadiene, and 9 ml. of diethylamine was left at 0° for 3 days. The mixture slowly darkened and a precipitate formed. After adding 50 ml. of water, the mixture was extracted several times with pentane. The combined extracts were washed with water until they were almost neutral and then dried over sodium sulfate. The pentane extracts were concentrated by careful fractionation when necessary. When ethanolamine was used as the base, 0.5 hr. was found sufficient for the reaction time. The extracts could be washed neutral more easily, but the product was less pure.

(Cyclopentadienylhydrazono)triphenylphosphorane (I).—Triphenylphosphine (26 g.) in 100 ml. of ether was added to a solution of diazocyclopentadiene in pentane prepared from 20 g. of *p*-toluenesulfonyl azide, and after a short time an orange-red precipitate started to separate. After filtration and drying, 25.5 g. (73%) of I, m.p. 121–123° (from dichloromethane–hexane), was obtained. From other batches we obtained I melting at 149–150°.[6] The infrared spectra were identical with the spectra given by Ramirez and Levy[3] and by Bestmann and Gothlich.[7]

Anal. Calcd. for $C_{23}H_{19}N_2P$: C, 77.95; H, 5.40. Found: C, 78.09; H, 5.54.

(Indenylhydrazono)triphenylphosphorane.—A solution of diazoindene in pentane was prepared, using a similar procedure as described earlier, from 11.6 g. of indene, 19.7 g. of *p*-toluenesulfonyl azide, and 10 ml. of diethylamine. Addition of 26 g. of triphenylphosphine to this solution yielded 10 g. (25%) of a yellow precipitate, which after recrystallization from benzene melted at 159–160°.

Anal. Calcd. for $C_{27}H_{21}N_2P$: C, 80.18; H, 5.24; N, 6.93; P, 7.44. Found: C, 80.48; H, 5.41; N, 6.96; P, 7.44.

Infrared (KBr): 3030 (m), 1523 (s), 1476 (m), 1446 (m), 1430 (s), 1353 (m), 1308 (m), 1218 (s), 1092 (vs), 1050 (m), 1003 (vs), 992 (vs), 912 (m), 846 (m), 788 (s), 748 (s), 712 (s), 637 (s), 620 (m), 612 (m). The infrared spectrum in chloroform was essentially the same and did not show additional bands due to dissociation, as reported for I.[7]

II (R = Me).—Dimethyl phosphite (40 ml.) was added to a solution of diazocyclopentadiene prepared from 84 g. of *p*-toluenesulfonyl azide. An oil immediately separated and, after some time, crystallized. Recrystallization from chloroform–ether yielded 25 g. of II (R = Me), white crystals, m.p. 174–175°. From the mother liquid 8 g. more of the compound was isolated (total yield, 25%).

Anal. Calcd. for $C_7H_{11}N_2O_3P$: C, 41.61; H, 5.49; N, 13.87; P, 15.32. Found: C, 41.81; H, 5.73; N, 14.05; P, 15.36.

Infrared (KBr): 3160 (m), 3000 (w), 2945 (m), 2845 (w), 1680 (w), 1610 (w), 1430 (s), 1320 (w), 1232 (2), 1178 (m), 1020 (vs), 946 (w), 925 (m), 880 (w), 830 (m), 775 (m), 753 (m), 712 (w), 660 (w), 640 (w), 604 (w).

II. (R = Et).—This compound was prepared analogously to the methyl ester. It had a m.p. 177–178° (from ethyl acetate–hexane).

Anal. Calcd. for $C_9H_{15}N_2O_3P$: C, 46.96; H, 6.57; N, 12.17; P, 13.48. Found: C, 46.85; H, 6.43; N, 12.69; P, 13.69.

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[1] To whom inquiries should be directed.

[2] W. von E. Doering and C. H. DePuy, *J. Am. Chem. Soc.*, **75**, 5955 (1953).

[3] F. Ramirez and St. Levy, *J. Org. Chem.*, **23**, 2036 (1958).

[4] H. Staudinger and O. Kupfer, *Ber.*, **44**, 3197 (1911).

[5] H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 619 (1919).

[6] Ramirez and Levy[3] reported a m.p. 121–122°, Bestmann and Gothlich[7] 151–153°. As we have observed both melting points it can be assumed that the compound exists in two modifications.

[7] H. J. Bestmann and L. Gothlich, *Ann.*, **656**, 1 (1962).