Bolliger and Prins[4] to give a crystalline mixture of the α- and β-anomers. It was therefore deemed necessary to prepare the pure α-anomer by hydrolyzing the methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside which was prepared according to the method of Bolliger and Prins.[4] A sirupy product, methyl 3-*O*-methyl-α-D-glucopyranoside, which crystallized as a hydrate, was obtained. The methyl 4,6-*O*-ethylidene-3-*O*-methyl-α-D-glucopyranoside derivative of the sirup was identical with the product described by Reeves,[2] thereby demonstrating the feasibility of using such a derivative for the separation of the pure α-anomer by fractional crystallization. In addition, the following crystalline derivatives were obtained: methyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranoside, methyl 3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside and methyl 2,4-di-*O*-acetyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.

Application of Hudson's isorotation rules to the α- and β-methylglucosides[5] of 3-*O*-methyl-D-glucose gave a difference for 2A of 38800, in agreement with the value obtained for other methylated glucosides and a sum for 2B of 28200, in agreement with the value of 26300 calculated from the rotations of the α- and β-anomers of 3-*O*-methyl-D-glucose.[6]

Experimental[7]

Methyl 3-*O*-Methyl-α-D-glucopyranoside.—A solution of 6.2 g. of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside[4] in 20 ml. of methanol was heated on the water-bath with 20 ml. of 0.01 *N* sulfuric acid for two hours. After cooling, the solution was treated with barium carbonate and the filtrate was concentrated *in vacuo*. The residual sirup was distilled at 120° under a pressure of 0.001 mm. to give 4.05 g. (95%) of a pale yellow sirup. *Anal.* Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75; OCH_3, 29.81. Found: C, 46.20; H, 7.78; OCH_3, 29.74.

After standing in contact with the atmosphere, the sirup crystallized. Recrystallization from cold ethyl acetate gave 3.90 g. of large prisms, m.p. 80–81°, corresponding to a hemihydrate. *Anal.* Calcd. for $C_8H_{16}O_6 \cdot {}^1/_2H_2O$: C, 44.23; H, 7.89; H_2O, 4.15. Found: C, 44.36; H, 7.50; H_2O, 4.17. The rotation was calculated for the anhydrous product, $[\alpha]^{21}D$ +164 ± 2° (in water, *c* 0.86).

Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranoside.—Sixty milligrams of crystalline methyl 3-*O*-methyl-α-D-glucopyranoside was dried and treated with 2 ml. of anhydrous pyridine and 1 ml. of acetic anhydride overnight at room temperature. The mixture was heated at 50° for one hour, cooled and poured on ice. After extracting with chloroform, then washing with dilute sulfuric acid, sodium bicarbonate and water, the chloroform extract was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residual sirup distilled at 120° under a pressure of 0.5 mm. to give a crystalline product. Recrystallization from a mixture of ether and petroleum ether gave 65 mg. (70%) of crystals, m.p. 71–72°, $[\alpha]^{21}D$ +113 ± 2° (in chloroform, *c* 1.86). *Anal.* Calcd. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63; OCH_3, 18.57. Found: C, 50.20; H, 6.64; OCH_3, 18.68.

Methyl 4,6-*O*-Ethylidene-3-*O*-methyl-α-D-glucopyranoside.—To a solution of 0.01 ml. of concentrated sulfuric acid in 3 ml. of paraldehyde was added 70 mg. of dry methyl 3-*O*-methyl-α-D-glucopyranoside. The mixture was shaken for two days, then water and petroleum ether were added. After shaking well, the aqueous layer was separated, and extracted twice with petroleum ether. The aqueous layer was then extracted with chloroform 4 times and the chloroform extracts were evaporated *in vacuo* to give 65 mg. (82%) of crystalline residue. It was dissolved in a mixture of benzene and hexane and chromatographed on alumina. Elution with mixtures of benzene and hexane gave crystalline fractions, which after recrystallization from a mixture of ether and petroleum ether melted at 106–107°, $[\alpha]^{21}D$ +150 ± 5° (in chloroform, *c* 0.46); $[\alpha]^{24}D$ +119 ± 5°, $[\alpha]^{24}_{4361}$ +240 ± 5° (in water, *c* 0.5).[8]

Methyl 3-*O*-Methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.—To a solution of 0.57 g. of dry methyl 3-*O*-methyl-α-D-glucopyranoside in 4 ml. of anhydrous pyridine was added 0.9 g. of triphenylchloromethane. The solution was heated at 100° for two hours. After cooling, the solution was treated with a small amount of ice, extracted with chloroform and the extracts washed with ice-cold dilute hydrochloric acid, dilute sodium carbonate and water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* left 1.5 g. of a yellow sirup, which was crystallized from benzene. Repeated recrystallizations gave 510 mg. (43%) of large prisms, m.p. 115–118°, $[\alpha]^{25}D$ +64 ± 2° (in chloroform, *c* 1.73). *Anal.* Calcd. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.68.

Methyl 2,4-Di-*O*-acetyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.—A solution of 2.25 g. of dry methyl 3-*O*-methyl-α-D-glucopyranoside was heated with 3.44 g. of triphenylchloromethane and 16 ml. of dry pyridine as described above; 32 ml. of dry pyridine and 15 ml. of acetic anhydride were then added and the solution left standing at room temperature for 24 hours. It was poured on ice and after 3 hours extracted with chloroform as described above. The sirup was dissolved in a mixture of benzene and hexane and chromatographed on alumina. Elution with mixtures of benzene and hexane gave crystalline fractions, which after recrystallization from methanol afforded 4.1 g. (70%) of prisms, m.p. 159–161°, $[\alpha]^{25}D$ +84 ± 2° (in chloroform, *c* 1.59). *Anal.* Calcd. for $C_{31}H_{34}O_8$: C, 69.95; H, 6.41. Found: C, 69.58; H, 6.46.

Acetylation of methyl 3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside gave a product identical by m.p. and mixed m.p. with the product described above.

(4) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(5) B. Helferich and O. Lang, *J. prakt. Chem.*, **132**, 321 (1932).

(6) J. C. Irvine and J. P. Scott, *J. Chem. Soc.*, **103**, 564 (1913); J. C. Irvine and T. P. Hog, *ibid.*, **105**, 1386 (1914); C. G. Anderson, W. Charlton and W. N. Haworth, *ibid.*, 1329 (1929).

(7) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954).

(8) Reeves[2] reported m.p. 106–107°, $[\alpha]^{25}D$ +114°, $[\alpha]^{25}_{4361}$ +246° (in water, *c* 0.6).

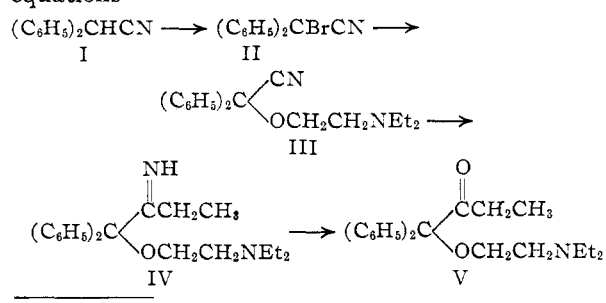
DEPARTMENT OF BIOLOGICAL CHEMISTRY,
HARVARD MEDICAL SCHOOL, AND
ROBERT W. LOVETT MEMORIAL FOUNDATION FOR
STUDY OF CRIPPLING DISEASES
MASSACHUSETTS GENERAL HOSPITAL
BOSTON 14, MASSACHUSETTS, AND
THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
SHREWSBURY, MASSACHUSETTS

1,1-Diphenyl-1-(β-diethylaminoethoxy)-2-butanone

BY PAULA KAUFMANN,[1] MILTON B. FRANKEL[2] AND HARRY S. MOSHER

RECEIVED JUNE 28, 1954

In the preparation of several diphenylmethane derivatives[3] difficulties were encountered in the preparation of 1,1-diphenyl-1-(β-diethylaminoethoxy)-2-butanone (V) by the steps indicated in the equations



(1) Parke, Davis and Co. Postdoctorate Fellow, 1953–1954.

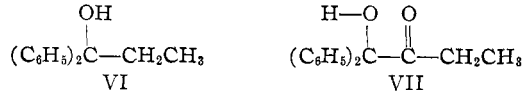
(2) Parke, Davis and Co. Research Fellow, 1947–1949.

(3) H. S. Mosher, M. B. Frankel and M. Gregory, THIS JOURNAL, **75**, 5326 (1953).

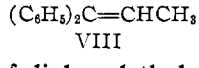
This compound possesses a certain structural relationship to the analgesic Amidone (Methadone) and a further investigation seemed desirable. No previous report of the preparation of α-bromodiphenylacetonitrile (II) was found in the literature, although the α-chlorodiphenylacetonitrile has been described[4] since this investigation was started.

The bromination of diphenylacetonitrile proceeded smoothly in carbon tetrachloride in the presence of acetic acid. Under a variety of other conditions the results were very erratic. In several preparations where the α-bromodiphenylacetonitrile (II) was not pure, it spontaneously lost bromine on standing and gave tetraphenylsuccinonitrile,[5] but the compound was reasonably stable when pure. The best yields (40%) of the 1,1-diphenyl-1-(β-diethylaminoethoxy)-acetonitrile (III) were obtained when the α-bromodiphenylacetonitrile (II) was added to an excess of sodium β-diethylaminoethoxide in excess β-diethylaminoethanol. Under other conditions considerable amounts of tetraphenylsuccinonitrile were formed.

The reaction of 1,1-diphenyl-1-(β-diethylaminoethoxy)-acetonitrile (III) with ethylmagnesium bromide, followed by hydrolysis with hydrochloric acid in ice, gave a mixture of the imine IV and the ketone V which could not be separated by simple distillation. The presence of the imine was indicated by the infrared spectra, which showed a significant band at 3.12 μ for the NH bond and another band at 6.04 μ characteristic of the C=N bond. In addition a crystalline picrate could be prepared from the mixture and this gave the analysis calculated for the picrate of IV. In all cases the percentage nitrogen in the distilled products was intermediate between that calculated for the imine IV and the ketone V. In one case the analysis indicated 85% imine and in another case 20% imine. When the hydrolysis was carried out with 0.1 *N* hydrochloric acid at room temperature for approximately one hour, a good yield of the desired ketone V could be obtained. If stronger hydrochloric acid was used in the hydrolysis of the crude mixture of IV and V, a nitrogen-free compound separated which was postulated to be 1,1-diphenyl-1-hydroxy-2-butanone (VII).



VI VII



VIII

A small yield of diphenylethylcarbinol (VI) also was isolated from the reaction mixture and its identity indicated by melting point, infrared spectra and analysis. In one of the Grignard reactions where the ether was replaced with benzene and the mixture refluxed for several hours, a 63% yield of 1,1-diphenyl-1-propene (VIII) was isolated. The carbinol VI can formally be considered to arise by the replacement of the nitrile group in III by the ethyl group of the Grignard reagent and hydrolysis of the β-diethylaminoethyl group; VIII is the dehydration product of VI.

(4) W. Wilson, *J. Chem. Soc.*, 2173 (1950).

(5) K. Auwers and V. Meyer, *Ber.*, **22**, 1227 (1889).

Experimental[6,7]

α-Bromodiphenylacetonitrile (II).—To a solution of 40 g. of diphenylacetonitrile (I) in 150 ml. of carbon tetrachloride and 5 ml. of acetic acid, 35 g. of bromine was added within a two-hour period. The reaction mixture was kept at a temperature of about 50°. After the addition of bromine was completed, the mixture was refluxed for three hours, until hydrogen bromide evolution had ceased, and then allowed to stand overnight. The solvent and the excess of bromine were evaporated under reduced pressure and the residual viscous liquid was washed twice with a solution of sodium bicarbonate, taken up in ether and washed with water until neutral. After drying with sodium sulfate and evaporation of the ether, the residual dark oil was distilled through a Vigreux column; 45 g. (80%) of a yellow oil, b.p. 120–125° (0.05 mm.), which solidified on cooling, was obtained. After recrystallization from petroleum ether (b.p. 55–85°) and isopropyl alcohol, white needles with a melting point range 33–38° were obtained.

Anal. Calcd. for $C_{14}H_{10}BrN$: C, 61.79; H, 3.70; N, 5.15. Found: C, 61.95; H, 3.73; N, 5.22.

1,1-Diphenyl-1-(β-diethylaminoethoxy)-acetonitrile (III).—β-Diethylaminoethanol (92 g.) and sodium (4 g.) were stirred together in a three-necked flask overnight at room temperature. After the sodium was dissolved, α-bromodiphenylacetonitrile (42 g.) was added at such a rate that the temperature of the reaction mixture did not exceed 50°. The stirring was continued for three hours at room temperature after which 50 ml. of dry benzene was added to the viscous mixture and the inorganic precipitate was removed by filtration. The benzene solution was washed three times with water, dried and distilled. After the solvent was removed, a yellow viscous oil, b.p. 148–152° (0.25 mm.), 19.2 g. (40%), $n^{20}D$ 1.5398, was obtained.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.80; H, 7.86; N, 8.95.

The picrate derivative of III was crystallized twice from ethanol, m.p. 122–125°.

The Reaction of 1,1-Diphenyl-1-(β-diethylaminoethoxy)-acetonitrile (III) with Ethylmagnesium Bromide.—A Grignard reagent was prepared from 1.9 g. of magnesium and 10 g. of ethyl bromide in 50 ml. of ether and cooled in an ice–salt mixture while 14.5 g. of the above 1,1-diphenyl-1-(β-diethylaminoethoxy)-acetonitrile (III), in 25 ml. of dry ether, was added dropwise over a period of one hour. After stirring at room temperature for five hours the reaction mixture was hydrolyzed by cooling to 0° and adding to a mixture of 15 ml. of concentrated hydrochloric acid in 15 g. of ice. The ether layer was washed immediately with water, the water layer washed with ether and the combined ether solutions were dried over sodium sulfate, evaporated on a steam-bath and the residue distilled at reduced pressure; 0.9 g. (9% yield based on formula VI), b.p. 140–143° (3 mm.), of a colorless oil which solidified on cooling was obtained. This compound was recrystallized from ethanol yielding colorless crystals, m.p. 92–95°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.68; H, 7.60. Found: C, 84.64; H, 7.65.

From analysis, melting point, nature of the reaction and infrared spectra this must be diphenylethylcarbinol (VI).[8]

The acid aqueous layer from the Grignard decomposition was made basic with a saturated soltuion of sodium carbonate and extracted with three 30-ml. portions of ether. The ether extracts were dried over sodium sulfate, evaporated, and the viscous, brown residual oil, was distilled through a small Vigreux column at reduced pressure to give 10.6 g. (74% yield based on formula IV), b.p. 156–162° (0.03 mm.), $n^{20}D$ 1.5456, of a viscous oil. The infrared spectrum of the reaction product shows a strong absorption band at 6.02 μ indicating a C=N group, weak absorption at 3.12 μ characteristic of NH group, and a band at 5.80 μ, indicating the presence of a C=O group.

Anal. Calcd. for IV, $C_{22}H_{30}N_2O$: C, 78.06; H, 8.92; N, 8.28. Calcd. for V, $C_{22}H_{29}NO_2$: C, 77.83; H, 8.61; N, 4.13. Found: C, 78.09; H, 8.88; N, 7.63.

On the assumption that the product is a mixture of IV and V, the nitrogen analysis indicates 85% imine.

(6) All melting points are uncorrected.

(7) Microanalysis by Microchemical Specialties Co., Berkeley, Calif.

(8) C. Hell and H. Bauer, *Ber.*, **37**, 231 (1904).

A picrate of the reaction product was made with a saturated solution of picric acid in ethanol and recrystallized three times from methanol, m.p. 175–178° dec.

Anal. Calcd. for $C_{22}H_{30}N_2O \cdot 2C_6H_6N_3O_7$: C, 51.25; H, 4.57; N, 14.06. Found: C, 51.70; H, 4.80; N, 14.06.

Apparently only the picrate of the imine IV was formed; the picrate of the ketone V, isolated below, is soluble in methanol.

1,1-Diphenyl-1-(β-diethylaminoethoxy)-2-butanone (V).—The mixed product from the above reaction (8.0 g.) was dissolved in 720 ml. of 0.1 *N* hydrochloric acid and allowed to stand at room temperature for one hour. The *p*H of the solution was approximately 3. After extracting the slightly turbid solution once with ether to remove any neutral product formed by hydrolysis, the acid layer was made basic with sodium carbonate and reextracted with ether. This ether extract was dried with sodium sulfate, the ether removed by heating on a steam-bath, and the residue distilled through a Vigreux column; b.p. 171–172° (3 mm.), 6.5 g., $n^{20}D$ 1.5388.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.83; H, 8.61; N, 4.13. Found: C, 78.01; H, 8.35; N, 4.19.

The infrared spectrum shows no absorption in the 2.80–3.20 μ region and shows strong absorption at 5.8 μ characteristic of the carbonyl band. No precipitate with picric acid could be obtained from an alcoholic solution; an oily picrate was formed from aqueous solution. In a preliminary run, similar to the above where the reaction mixture was refluxed in benzene, a 63% yield of a hydrocarbon, identified as unsymmetrical methyldiphenylethylene (VIII),[9] m.p. 50°, was isolated.

The mixed product IV and V, 1.5 g., was dissolved in 6 *N* hydrochloric acid; after standing a few minutes at room temperature the solution became cloudy, and an oil separated. The mixture was warmed on the steam-bath for two hours and the oil which separated was extracted with ether and distilled to give 0.56 g. of a yellow oil, b.p. 110–120° (2 mm.), $n^{20}D$ 1.5850. This is a neutral compound which does not contain nitrogen and shows strong infrared bands at 2.90 and 5.84 μ characteristic of hydroxy and carbonyl groups. It is postulated to be the hydroxy ketone VII, but its identity was not investigated further.

(9) A. Klages, *Ber.*, **35**, 2647 (1902).

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
STANFORD UNIVERSITY
STANFORD, CALIFORNIA

Studies with N-Halo Reagents. II. New Syntheses of β-Bromo-α-keto Esters, Ethyl Phenylglyoxylate and Phenacyl Bromide Using N-Bromosuccinimide[1]

BY PAUL F. KRUSE, JR., NATHAN GEURKINK AND KEN L. GRIST

RECEIVED JUNE 24, 1954

The reactions of hydroxy compounds with N-bromosuccinimide were reviewed briefly by Barakat and El-Wahab[2] in their recent account of the degradation of aliphatic α-hydroxy acids with this reagent. The report[3] on the oxidation of alcohols with N-bromosuccinimide led us to investigate reactions of this reagent with α-hydroxy esters as a route to the synthesis of α-keto esters and thence to α-keto acids. Since the α-hydroxy esters were soluble in carbon tetrachloride, we have used it as the reaction medium rather than the aqueous media reported in the studies referred to above.

This study has shown that: (a) the reaction of equimolar amounts of ethyl lactate with N-bromosuccinimide resulted in a mixture of the α-keto ester, ethyl pyruvate and the β-bromo-α-keto ester, ethyl bromopyruvate; this makes the α-hydroxy ester–N-bromosuccinimide reaction generally unattractive for the preparation of unsubstituted α-keto esters (and acids); (b) the 1:2 (or slightly less) mole ratio reactions of ethyl lactate, ethyl DL-α-hydroxybutyrate and ethyl DL-α-hydroxyhydrocinnamate with N-bromosuccinimide gave 64, 66 and 71% yields of the respective β-bromo-α-keto esters; and (c) the reaction of equimolar amounts of ethyl mandelate with N-bromosuccinimide gave ethyl phenylglyoxylate in 79% yield.

Result (b) constitutes a new method of preparing β-bromo-α-keto esters. These esters hydrolyze easily in the cold and thereby are converted to the corresponding β-bromo-α-keto acids. The method is a useful one since α-hydroxy esters are quite readily obtainable in contrast to α-keto esters and acids, which have been employed as starting materials for the preparation of β-bromo-α-keto esters[4] and acids.[5] These results with α-hydroxy esters suggest a number of possibilities of converting hydroxy compounds to α-bromocarbonyl compounds in one easy step.

Result (c) represents a new synthesis of the α-keto ester, ethyl phenylglyoxylate. For cases such as this, where β-bromination cannot occur, the equimolar reaction would be satisfactory for the preparation of α-keto esters, and respectively, acids. The synthesis of ethyl phenylglyoxylate from ethyl mandelate and N-bromosuccinimide appears simpler than by the permanganate oxidation method,[6] the selenium dioxide oxidation of ethyl phenylacetate,[7] the ethyl chloroglyoxylate–benzene condensation[8] or the lead tetraacetate oxidation of methyl mandelate.[9]

An additional study of the one-step hydroxy to α-bromocarbonyl synthesis comprised treating DL-phenylmethylcarbinol with two moles of N-bromosuccinimide. Phenacyl bromide was obtained in 44% yield. Improvements in the synthesis were not investigated.

Experimental[10]

Ethyl Bromopyruvate (I).—To a solution of 5.00 g. (0.042 mole) of freshly distilled ethyl lactate in 75 ml. of C.P. carbon tetrachloride there was added 14.24 g. (0.080 mole) of N-bromosuccinimide. The mixture was refluxed for six hours, during which time a deep red bromine color was dissipated and hydrogen bromide was evolved. The mixture was cooled and filtered with suction to yield 8.1 g. (*ca.* 102%) of crude succinimide. The filtrate was concentrated on a steam-bath to 15 ml., dried over anhydrous sodium sulfate and distilled *in vacuo* from a small modified Claisen flask to yield 5.25 g. (64%) of I, b.p. 83–88° (8 mm.),[11] $n^{24}D$ 1.469, d^{24}_{20} 1.561; MR_D calcd. 34.7, found 34.8.

(1) Presented in part at the Southwest–Southeast Regional Meeting, American Chemical Society, New Orleans, La., December 10, 1953.

(2) M. Z. Barakat and M. F. A. El-Wahab, THIS JOURNAL, **75**, 5731 (1953).

(3) M. Z. Barakat and G. M. Mousa, *J. Pharm. and Pharmacol.*, **4**, 115 (1952).

(4) P. Siefert, E. Vogel, A. Rossi and H. Schinz, *Helv. Chim. Acta*, **33**, 725 (1950).

(5) D. B. Sprinson and E. Chargaff, *J. Biol. Chem.*, **164**, 417 (1946).

(6) H. Gilman and A. H. Blatt (Editors), "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 2nd ed., 1946, p. 241.

(7) J. Vene, *Bull. soc. chim.*, **12**, 506 (1945); *C. A.*, **40**, 4661 (1946).

(8) K. Kinder, W. Metzendorf and Dschi-yin-Kwok, *Ber.*, **76B**, 308 (1943); *C. A.*, **37**, 5710 (1943).

(9) E. Baer and M. Kates, THIS JOURNAL, **67**, 1482 (1945).

(10) All m.p.'s and b.p.'s reported herein are uncorrected.

(11) S. Archer and M. G. Pratt, THIS JOURNAL, **66**, 1657 (1944); b.p. 116–121° (27 mm.) and redistilled for analysis, b.p. 92.5–94.0° (10 mm.).