TABLE I

PREPARATION OF 3-SUBSTITUTED-2,5-OXAZOLIDINEDIONES

3-Substituent	Yield, %[a]	Solvent[b]	M.P., °C.[c]	Calculated C	Calculated H	Calculated N	Calculated Mol. Wt.	Found C	Found H	Found N	Found Mol. Wt.[d]
p-$HOOCC_6H_4$—	20	T	ca. 236[e]	54.33	3.20	6.33	221	54.52	3.70	6.27	255
p-$NO_2C_6H_4$—	45	T or D	193–195	48.65	2.72	12.61	222	47.93	2.41	12.42	223
p-$CH_3COC_6H_4$—	40	T or D	170			6.40	219			6.35	218
CH_3CO—	32	E	138	41.27	3.52	9.78	143	41.64	3.76	9.55	142
p-CNC_6H_4—	12[f]	E	167			13.86				13.87	

[a] Yield of pure material. [b] Solvent for recrystallization, used with petroleum ether; T = tetrahydrofuran, D = dioxane, E = ethyl acetate. [c] All substances melted with decomposition. [d] From neutral equivalent. [e] Decomposition not sharp, beginning at this temperature. [f] Yield could be improved by continuous extraction with ethyl acetate.

fact that 3-*p*-tolyl-oxazolidinedione was satisfactorily prepared by Fuchs.[4] Subsequent work showed that, when strongly electron-attracting substituents were present on the nitrogen, the oxazolidine ring was formed with moderate ease. Five examples of compounds of this type are given in Table I.

These oxazolidinediones showed no tendency to form polymers in the presence of water as initiator. This is parallel to the reluctance to polymerize of the higher N-alkyl derivatives studied by Wessely, Riedl, and Tuppy.[7]

EXPERIMENTAL

Known N-substituted glycine derivatives. N-Acetylglycine was obtained by Dakin's method.[10] N-*p*-Carboxyphenylglycine, prepared by the method of Mauthner and Suida,[11] had a melting point (258°) in agreement with that of Takeda and Kuroda[12] (255°), not that of the former authors (219–221°). N-*p*-Nitrophenylglycine[13] was most conveniently prepared from bromoacetic acid, previously used only for the ortho isomer.[14]

N-p-cyanophenylglycine. A solution of 6.0 g. (0.05 mole) of recrystallized *p*-aminobenzonitrile and 10 g. (0.11 mole) of chloroacetic acid in 150 cc. of hot water was refluxed until the product began to separate out. On cooling, 4.3 g. of product (49% yield) was obtained, m.p. 234° after washing with ether and recrystallizing twice from water.

Anal. Calc'd for $C_9H_8N_2O_2$: N, 15.91. Found: N, 15.69, 15.83. Alcoholysis gave the known *p*-carbethoxyphenylglycine ethyl ester.[15]

N-p-acetylphenylglycine. A mixture of 2 g. (0.0148 mole) of *p*-aminoacetophenone and 2 g. (0.0144 mole) of bromoacetic acid was heated at 100–115° for 20 min., then cooled and treated with 100 ml. of 3*M* ammonium hydroxide. After standing for 12 hr., the ammonia solution was filtered, the insoluble part reextracted with ammonia, and the product precipitated from the extracts with concentrated hydrochloric acid; m.p. 225° with decomposition, yield 22%.

Anal. Calc'd for $C_{10}H_{11}NO_3$: N, 7.25; neut. equiv., 193. Found: N, 7.24; neut. equiv. 195.

N-p-anisyl-N-chlorocarbonylglycine. Phosgenation of N-*p*-anisylglycine[16] (0.05 mole) in dioxane gave a 36% yield of this substance, m.p. 131–132° after separation from unreacted N-*p*-anisylglycine with ether and recrystallization from ethyl acetate by adding petroleum ether.

Anal. Calc'd for $C_{10}H_{10}ClNO_4$: N, 5.75. Found: N, 5.86, 5.79. The substance did not undergo ring closure by heating at 40°.

Oxazolidinediones. The N-substituted amino acid (0.01 to 0.03 mole), suspended in about 250 ml. dioxane, was treated with phosgene for 2 to 4 hr. at room temperature, except for the last two substances in Table I, which required a temperature of 40–45°. After the amino acid had dissolved, the solvent was removed at 35–40° and 2 mm., and the residue crystallized from a suitable solvent by the addition of low-boiling petroleum ether. Under these conditions N-*o*-nitrophenylglycine did not react with phosgene.

All the oxazolidinediones gave an immediate reaction with aniline with the evolution of carbon dioxide. However, when the compounds were exposed to moisture at room temperature or at 100–135°, polymers were not formed. On standing in air-filled, closed specimen bottles for a year, the *p*-nitrophenyl-, *p*-cyanophenyl- and *p*-acetophenyl-oxazolidinediones reverted to the original free acids, and the *p*-carboxyphenyl derivative was partly converted. The N-acetyloxazolidinedione was stable under these conditions.

Determination of oxazolidinediones by acidimetry. The possibility of analysis by the neutral equivalent was tested[17] on four of the oxazolidinediones. Three of these reacted rapidly with aqueous base, giving results having an accuracy of ±0.5% (shown as molecular weights in Table I). Samples varying from 10 to 100 mg. were dissolved in an excess of 0.1*N* sodium hydroxide, which was back-titrated with standard hydrochloric acid to the phenolphthalein endpoint. A blank titration was also run. When applicable, this method requires fewer special solutions than the sodium methylate titration of Berger, Sela, and Katchalski.[18]

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(14) J. Plöchl, *Ber.*, **19**, 7 (1886).

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Cyclodehydrations in Liquid Sulfur Dioxide

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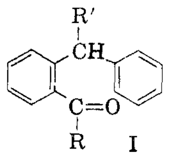
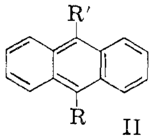
Phosphorus pentoxide has long been used as a cyclizing agent, commonly in suspension in boiling benzene or toluene. It is usual that the phosphorus pentoxide in such a medium forms a sticky coagulum[1] which adheres to the reaction vessel and fairly effectively removes itself from the sphere of the reaction. While this difficulty is somewhat mitigated by the use of a dispersing agent such as Filter-Cel,[1] it is by no means eliminated.

We have found that with vigorous stirring, phosphoric anhydride can be maintained in a fairly fine suspension in liquid sulfur dioxide. Despite the low temperature of this mixture (−10°), it is effective in bringing about the aromatic cyclodehydration of some *o*-benzylbenzophenones (I). As ordinarily carried out, the cyclization I → II appears to be acid-catalyzed[2] and is usually thought of as involving a conjugate acid formed by addition of a proton to the ketone (I).[3–5] One would expect that a Lewis acid could function in the place of a proton, and would add the present cyclization to the growing list of instances in which phosphorus pentoxide has been found to function in the manner expected of a Lewis acid.[6]


I


II

The cyclization selected for detailed study was that of *o*-benzylbenzophenone[7] (I, R = C_6H_5; R′ = H) to yield 9-phenylanthracene (II, R = C_6H_5; R′ = H), and detailed results may be seen in Table I.

It will be seen that an insignificant increase in yield is effected by increasing the time of reaction or the quantity of phosphoric anhydride used, and in each case, ketone was usually recovered. It was not found beneficial to add the pentoxide at 1-hr. intervals. Sulfur dioxide which had been predried over phosphorus pentoxide worked no better than the commercial grade; addition of a small amount of water, however, stopped the cyclization. When the reaction was carried out at room temperature by use of a sealed tube, it gave an unidentified black solid plus some unreacted ketone. Finally, the addition of various reagents including trifluoroacetic acid and anisole was without benefit.

TABLE I

CYCLIZATION OF *o*-BENZYLBENZOPHENONE

P_2O_5, g.[a]	Time, Hr.	Conditions	Phenyl-anthracene, %[b]
2	2	...	50
2	3	...	52
2	6	...	59
5	2	...	59[c]
5	6	...	57.5[d]
4[e]	4	Portionwise addition	58
0.5	2	...	[f]
5[g]	2	Dry SO_2	53
2[h]	2	H_2O	...[i]
2[j]	19	Room temperature	...[k]
5[l]	2	CH_3COOH	...[m]
5[n]	2	$CH_3OC_6H_5$	44[c]

[a] In all runs, 500 mg. of *o*-benzylbenzophenone was used. [b] Except as noted, all yields are for products melting not lower than 150° (lit.[7] 154–155°). [c] Average of two runs. [d] M.p. 149–152°. Evaporation of the mother liquor yielded 110 mg. of material (m.p. 45–52°) which was probably impure ketone (m.p.[7] 50–52°). [e] One gram of phosphorus pentoxide was used at the start, and then one gram added hourly. [f] No hydrocarbon was isolated. The product melted at 49–52°. [g] Liquid sulfur dioxide was dried over phosphorus pentoxide and then distilled into the reaction vessel. [h] Six drops of water added. [i] The ketone (500 mg.), m.p. 49–52°, was recovered. [j] The reaction was carried out in a sealed tube which was rotated at room temperature for nineteen hours. Only 30 ml. of liquid sulfur dioxide was used. [k] A considerable quantity of an unidentified black carbon tetrachloride–insoluble product was formed. No hydrocarbon was insolated. [l] Trifluoroacetic acid (13 ml.) was added. [m] Only 57 mg. of impure material was obtained, m.p. 130–140°. While this could have contained some hydrocarbon, the over-all yield in the reaction must be less than 12%. [n] Anisole (12 ml.) was added.

It was a consistent observation that a sizable fraction of the starting material could not be accounted for either as recovered starting material or as product. When pure 9-phenylanthracene was exposed to the action of phosphorus pentoxide for 2 hr. under the conditions of the reaction, only 81% of it could be recovered and a portion of this appears to have been lost as a water-soluble fraction.[8]

The new cyclodehydration medium was tried with several additional ketones and the results are shown in Table II.

The behavior of the last two ketones (I) deserves some comment. The 2-benzyl-4′-cyanobenzophenone (I, R = p-C_6H_4CN; R′ = H) which failed to cyclize with phosphorus pentoxide is converted to 9-(p-carboxyphenylanthracene by the ac-

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(1) Johnson, *Org. Reactions*, **2**, 170 (1944).

(2) The recently announced discovery [Vingiello and Borkovec, *J. Am. Chem. Soc.*, **78**, 3205 (1956)] that cyclizations of this type may be carried out by heating the ketones (I) with activated alumina may indicate the possibility of another pathway for the reaction.

(3) Berliner, *J. Am. Chem. Soc.*, **64**, 2894 (1942).

(4) Bradsher and Smith, *J. Am. Chem. Soc.*, **65**, 854 (1943).

(5) Bradsher and Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949).

(6) *E.g.*, Lecher, *Ber.*, **46**, 2664 (1913); Steinkopf, *Ann.*, **413**, 343 (1917); Steinkopf and Schubert, *Ann.*, **424**, 1 (1921); Hartough and Kosak, *J. Am. Chem. Soc.*, **69**, 3098 (1947); Perfetti and Levine, *J. Am. Chem. Soc.*, **75**, 626 (1953); Luder and Zuffanti, *The Electronic Theory of Acids and Bases*, John Wiley and Sons, Inc., New York, N. Y., 1946, pp. 116, 132.

(7) Bradsher, *J. Am. Chem. Soc.*, **62**, 486 (1940).

(8) The recent observation [Lecher, Chao, Whitehouse, and Greenwood, *J. Am. Chem. Soc.*, **76**, 1045 (1954)] that benzene heated at 275° with P_2O_5, followed by hydrolysis, produced phenylphosphonic acid in good yield, suggests the possibility that the much more reactive anthracene nucleus might be attacked similarly at a much lower temperature. It is also possible that a polar solvent, such as sulfur dioxide might favor the attack on the aromatic nucleus.

TABLE II

CYCLIZATION OF OTHER *o*-BENZYLPHENONES (I)

R′	R	P_2O_5, g.[a]	Yield II, %
C_6H_5	C_6H_5[b]	2	48.5[c]
C_6H_5	C_6H_5	5	60[d]
H	p-C_6H_4Cl[e]	5	44[f]
H	p-C_6H_4CN[g]	4[h]	. . .[i]
H	p-$C_6H_4OCH_3$	5[j]	60[k]

[a] Except as noted, 500 mg. of ketone was used. [b] Bradsher and Smith, *J. Am. Chem. Soc.*, 65, 451 (1943). [c] M.p. 245–247° (lit.[b] 245–247°). [d] M.p. 240–243.5°. [e] Ref. 5. [f] M.p. 176.5–179° (lit.[5] 179–180°). In addition, 97 mg. of ketone, m.p. 72–73° (lit.[9] 73°) was recovered. [g] Ref. 9. [h] Reaction using 370 mg. of ketone. [i] Ketone (258 mg.) was recovered, m.p. 103.5–105° (lit.[9] 104.5–105°). [j] M.p. 69–70°, Ref. 10. [k] Yellow shiny needles, m.p. 165.5–166.5°. The analytical sample, crystallized from ethanol, melted at 168–168.5°. *Anal.* Calc'd for $C_{21}H_{16}O$: C, 88.73; H, 5.65. Found: C, 89.03; H, 6.05.

tion of hydrobromic and acetic acids.[9] The attempted cyclization of 2-benzyl-4′-methoxybenzophenone (I, R = p-$C_6H_4OCH_3$; R′ = H) with hydrobromic and acetic acids yielded only an impure brown oil.[10]

In a single preliminary experiment, it was shown that the dehydration of *o*-benzylbenzoic acid to anthrone could be brought about in 39% yield using the sulfur dioxide medium. While the sulfur dioxide–phosphorus pentoxide combination, when used in the cyclization of *o*-benzyl phenones, gives a yield almost consistently poorer than that obtained with the boiling hydrobromic-acetic acid mixture, the low temperature at which cyclodehydration occurs in the sulfur dioxide medium makes it of possible interest in cyclizations involving heat-sensitive compounds.

EXPERIMENTAL

General procedure. The entire apparatus, consisting of a 200 ml. 3-necked flask with a mechanical stirrer and dry ice condenser fitted with a calcium chloride tube, was dried by heating with a flame before use. About 50 ml. of liquid sulfur dioxide from a tank was run into the flask and the ketone (usually 500 mg.) was added. Stirring was begun and the phosphorus pentoxide added. The reaction mixture (usually yellow) was mechanically stirred for several hours, at the end of which about 20 ml. of carbon tetrachloride was added. The mixture was allowed to stand until the ice first formed had melted, and most of the sulfur dioxide had evaporated. The carbon tetrachloride and water layers were separated, and the water washed twice more with carbon tetrachloride. The carbon tetrachloride layer was washed three times with water, dried over calcium chloride, and then concentrated. Ethanol was added to the concentrate and the solution concentrated further to remove the carbon tetrachloride and to induce crystallization.

Effect of the cyclizing medium upon 9-phenylanthracene. The reaction vessel was charged with 50 ml. of liquid sulfur dioxide and 467 mg. of 9-phenylanthracene (theoretical yield from 500 mg. of ketone), and 2 g. of phosphorus pentoxide. The mixture was stirred for 2 hr. and worked up in the usual way. In two runs, the yield was 373 mg. (80%), m.p. 151–153.5° in the first and 384 mg. (82%), m.p. 151–154.5° in the second. Evaporation of the mother liquors yielded a dark reddish brown material (50 mg.; 26 mg.).

Cyclization of o-benzylbenzoic acid. One-half gram of *o*-benzylbenzoic acid[11] in 50 ml. of sulfur dioxide was stirred for 2 hr. with 5 g. of phosphorus pentoxide and the mixture worked up as in the standard procedure. Light yellow needles of 9-anthrone were obtained, m.p. 152–154° (lit.[12] 154°); yield, 176 mg. (39%).

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(10) F. A. Vingiello, Ph.D. thesis (1947).

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Symmetrical N,N,N′,N′-Tetraalkylpiperazinium Di-alkylsulfates

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Smith, Curry, and Eifert[1] have described the preparation of a series of symmetrical N,N′-dialkylpiperazines, in which the alkyl groups were *n*-octyl, *n*-decyl, *n*-dodecyl, *n*-tetradecyl, and *n*-hexadecyl. From them they prepared the corresponding dihydrobromides, N,N′-dialkyl-N,N′-dimethylpiperazinium di-methiodides and N,N′-dialkyl-N,-N′-diethyl-piperazinium di-ethiodides. They described one piperazinium di-alkylsulfate, N,N′-di-*n*-tetradecyl-N,N′-dimethyl-piperazinium di-methylsulfate.

Extending our studies in the fields of morpholinium and thiamorpholinium alkyl sulfates[2] the above series of symmetrical N,N′-dialkylpiperazines has been lengthened to include N,N′-di-*n*-octadecylpiperazine and two series of N,N′-dialkyl-N,N′-dimethyl-piperazinium di-methylsulfates and N,N′-dialkyl-N,N′-diethyl-piperazinium di-ethylsulfates have been prepared.

EXPERIMENTAL

N,N′-Dialkylpiperazines were prepared by refluxing 0.05 mole of anhydrous piperazine (Bios Laboratories, Inc.) with 0.12 mole of alkyl bromide in 30–40 ml. of absolute alcohol for 18–24 hr. After cooling, the resultant salt was filtered and redissolved in alcohol. The solution was made alkaline with dilute sodium hydroxide and the resultant precipitate of the free amine was filtered, washed with water, refiltered, and, after air drying, was recrystallized from ethyl acetate. The dialkylpiperazines are white waxy solids, insoluble in water and only slightly soluble in cold alcohol and ethyl acetate. The yields obtained varied from 55% to 85%. The melting points were in substantial agreement with those given by Smith, Curry, and Eifert.[1] N,N′-di-*n*-octadecylpiperazine melts at 97–98°C., uncorr.

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